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ORIGINAL ARTICLES.

OBSERVATIONS ON THE PATHOLOGIC PHYSIOLOGY OF THE INSULAR AND EXTERNAL SECRETORY FUNCTIONS OF THE HUMAN PANCREAS.

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This report includes observations on three series of patients and illustrates the effect of abnormal conditions of the pancreas on its external and internal secretory functions. The first group includes cases of hyperinsulinism due to tumor of the islands of Langerhans; the second consists of 3 cases of hyperinsulinism that had three-quarters of the pancreas removed, and the third group, 3 patients that had the head of the pancreas removed for carcinoma.

I. We believe that it is of interest to tabulate the glucose tolerance figures in our relatively large series of cases of hyperinsulinism before and after removal of histologically verified tumors of the islands of Langerhans and to plot curves of their mean values (Table 1 and Charts 1 and 2).

While the charts vary considerably, there is a decided trend towards a diabetic curve. In some cases this tendency is present 1 year after the tumor has been removed. The cause is purely conjectural at the present time. However, one may assume that overproduction of insulin by the tumor depresses its formation by the remainder of the islands, resulting in a relative insufficiency of insulin. Due to the increased oxidation of glucose, disturbances in glycogen storage may also be a factor. The Conns[4] speak of a

fasting blood sugar level of 310 mg. per 100 cc. several weeks after the removal of an adenoma causing hyperinsulinism.

A somewhat analogous reaction is observed clinically in cases of hypothyroidism. If one withholds thyroxin after it has been given in sufficient quantity to restore normal metabolism, the basal metabolic rate may decrease to a point considerably below what it was at the outset.

The average minimum blood sugar in this series was 38. It is obvious that the glucose tolerance test is not as decisive in the diagnosis of hyperinsulinism as is the constant occurrence of low fasting blood sugars, associated with loss of consciousness or other severe nervous derangement and the prompt recovery on the exhibition of sugar.

II. In 3 cases of hyperinsulinism in which no tumor was found at operation, three-quarters of the pancreas was resected in order to decrease the supply of insulin. This, however, was ineffectual. At a subsequent operation the duodenum was mobilized and the adenoma was found and removed.

Case Notes. Case 1.—Z. G. No. 512939. Age 45. At the second operation the pancreatic remains measured 4 by 3 by 2 cm. The dextrose tolerance test was as follows:

Blood Sugars After Ingestion of Dextrose.

Fasting.	½ hour.	1 hr.	2 hr.	3 hr.	Time after removal of adenoma.
108	141	163	137	..	10 days
95	..	..	167	142	3 months
90	166	178	133	127	30 months

Her fasting blood sugars since have varied between 81 and 113 and she has had no symptoms of insulin shock or diabetes.

Case 2.—I. M. No. 530663. Age 22. Similar to Case 1. Dextrose tolerance test after removal of the adenoma was as follows:

Blood Sugars After Ingestion of Dextrose.

Fasting.	½ hr.	1 hr.	2 hr.	3 hr.	Time after removal of adenoma.
119	153	153	152	149	18 days
103	..	127	109	..	28 months

Case 3.—E. S. No. 475076. Age 30. Similar to the foregoing cases in all respects. The dextrose tolerance test after operation was as follows:

Blood Sugars After Ingestion of Dextrose.

Fasting.	½ hr.	1 hr.	2 hr.	3 hr.	Time after removal of adenoma.
122	237	282	233	288	2 weeks
110	..	190	278	200	6 weeks

In this group after operation the same tendency to delayed removal of glucose from the blood is manifest, but it is remarkable that after a time (about 2 years or sooner) glucose utilization

TABLE 1.—BLOOD SUGARS AFTER INGESTION OF 100 GRAMS OF DEXTROSE BY MOUTH IN 17 CASES OF TUMOR OF THE ISLANDS OF LANGERHANS.

Hist. No.	Time of test.	Fasting.	½ hour.	1 hour.	2 hour.	3 hour.	Remarks.
540606	Before operation	26*					
	Before operation	35	93	91	142	94	
	Before operation	35	103	147	163	141	
	Before operation	40	..	166	200	100	
554410	Before operation	33*	..	..	..	..	At operation adenoma together with tail and part of body of pancreas removed.
	Before operation	71	143	154	170		
	Before operation	55	148	167	127		
	15 days after operation	95	174	229	234	90	
	75 days after operation	89	118	117	81	75	
	9 mos. after operation	88	165	190	170	104	
592078	Before operation	40*					
	Before operation	40	147	110	131		
	30 days after operation	129	181	220	209		
	11 mos. after operation	102	185	200	181	80	
389424	Before operation	30*					
	Before operation	30	34	101	147		
	Before operation	35	132	135	119		
	9 days after operation	100	145	..	230		
	16 days after operation	91	180	176	130		
530663	Before operation	27*					
	Before operation	64	..	86	115		
350794	Before operation	47*					
	Before operation	58	104	130	119		
	8 mos. after operation	87	111	133	95	70	
475076	Before operation	20*					
	Before operation	33	176	188	197		
512939	Before operation	30*					
	Before operation	85	154	235	246		
546637	Before operation	37*					
	Before operation	48	108	96	246	203	
	Before operation	36	110	85	156		
	Before operation	46	91	97	158	165	
	18 days after operation	106	..	160	189	150	
434383	Before operation	30*	..	..	..	..	Part of body and tail of pancreas removed with tumor.
	Before operation	64	108	..	133		
	16 days after operation	90	..	207	207		
	14 mos. after operation	97	253	212	163		
306695	Before operation	38*					
	22 days after operation	61	164	171			
583382	Before operation	33*					
	Before operation	42					
	11 days after operation	105	170	..	115		
563920	Before operation	45*					
	Before operation	74	180	258	252	170	
	Before operation	45	89	92	90		
510933	Before operation	54*					
	Before operation	60	95	167	182	103	
	Before operation	60	133	153	133	173	
	Before operation	59	132	232	194	168	
428308	Before operation	57*					
	Before operation	57	102	78	65	68	
421465	Before operation	43*					
	Before operation	52	130	105	162		
605580	Before operation	35*					
	Before operation	64	98	125	122	83	

* Minimum.

assumes the normal rate in spite of the absence of three-quarters of the pancreas. Obviously, the human pancreas, like the kidneys and the liver, has an enormous functional reserve.

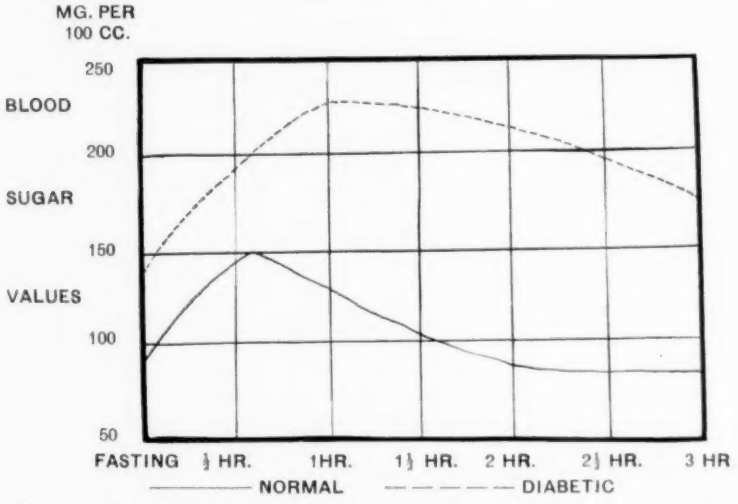

CHART 1.—Diabetic and normal blood sugar assimilation curves after 100 gm. of glucose by mouth.

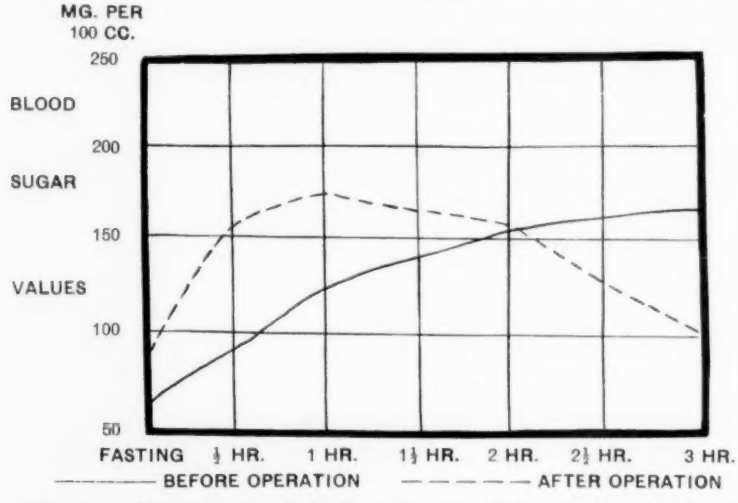

CHART 2.—Mean glucose assimilation curves after 100 gm. of glucose by mouth in 17 cases of hyperinsulinism due to tumors of the islands of Langerhans.

III. The absence of pancreatic juice in the intestine of dogs leads to wide variations in fat absorption[5] that are unexplained at the present time. The stomach and small intestine secrete weakly active lipases and it is conceivable that a compensatory increase in

their activity occurs when pancreas lipase is unavailable. The bile also contains a weak lipase. However, Koskowski and Ivy's work on depancreatized dogs with fistulæ of the small intestine[8] does not support this idea. In dogs with isolated intestinal loops (Thiry-Vella fistula) Jansen[7] demonstrated a weak lipase active at about the neutral point.

Ralli *et al.*[9] observed that 3 normal dogs absorbed 97% and 95% of ingested fat and protein; but after ligation of their pancreatic ducts, fat absorption was reduced to 71%, 71% and 47% and protein absorption to 73%, 72% and 33% respectively. Selle and Moody[11] found an average fat absorption of 75% in 4 pancreatectomized dogs. This was unimproved by the administration of dried

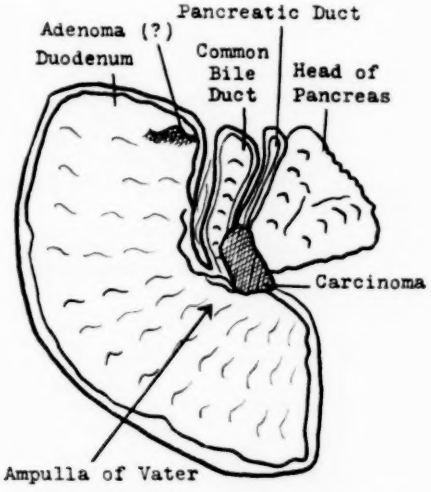

FIG. 1.—Carcinoma of the ampulla of Vater.

pancreas. In 7 dogs deprived of pancreatic secretion, Schmidt *et al.*[10] noted a 60% improvement in fat and protein absorption after feeding dried pancreas. They gave as much as 25 gm. of the dry powder to dogs weighing from 11 to 14 kilos.

In the human, clinicians have attached considerable importance to the activity of the pancreas in the digestion and absorption of fats.

One author states that the absence of pancreatic secretion from the intestine results in bulky, soft, light-colored and highly fatty stools.[6] Another source, however, says that "there is evidence to show that a substitute for pancreatic juice may, if necessary, be manufactured by other digestive glands in the duodenum, especially Brunner's glands. Thus, the suppression of the pancreatic juice may result in only temporary difficulties. The development of frequent fatty, gray stools is supposed to be due to interference with normal secretion and is called pancreatogenous diarrhea."[3] A third

TABLE 2.—CASE 1.

M. J. Age 49. History 440080.
Diagnosis: Carcinoma of ampulla of Vater.
First operation: January 25, 1935. Gastro-enterostomy.
Cholecystgastrostomy.
Ligation of common bile duct.
Second operation: February 7, 1935. Removal of duodenum and part of pancreas.
Death: Metastatic carcinoma. April, 1937.

DAILY FAT ABSORPTION IN THE ABSENCE OF PANCREATIC JUICE.
(Daily Fat Ingestion, 100 Grams.)

Date, 1935.	24 hr. stool contained (gm.)	Per cent fat absorption.
2/19	11.0	80.0
2/20	7.0	93.0
4/9	11.2	88.8
10/19	5.6	94.4
10/20	7.6	92.4
10/21	3.2	96.8

NOTE.—On October 19 the gastric contents contained no pepsin or acid but considerable trypsin and some lipase.

TABLE 3.—CASE 2.

E. W. Age 53. History 422738.
Diagnosis: Carcinoma papilla Vater.
First operation: July 18, 1934. Cholecystgastrostomy.
Second operation: August 21, 1934. Partial pancreatectomy, partial duodenectomy. Duodenoduodenostomy.
Death: Due to biliary tract infection. April 16, 1935.
Autopsy: No pancreatic communication with small intestine could be demonstrated.

DAILY INTESTINAL ABSORPTION IN THE ABSENCE OF PANCREATIC JUICE.

	Daily ration (gm.).		Stool contained (gm.).		% absorption.	
Date, 1934.	Protein.	Fat.	Protein.	Fat.	Protein.	Fat.
9/8	60	40	9.7	14.4	84.0	64.0
9/9	60	40	6.9	14.6	88.5	63.0
9/10	60	40	12.6	26.7	79.0	33.0
9/15	72	41	1.2	0.6	98.5	98.5
9/16	70	39				
*9/17	51	34	31.1	16.9	39.0	50.0
*9/18	63	43				
*9/19	64	40				
*9/20	66	40	26.0	15.3	60.6	61.7
*9/21	70	40				
*9/28	70	40	6.8	7.5	90.0	81.0
*9/29	70	40	16.9	18.4	76.0	54.0
*9/30	70	40	14.5	16.9	79.0	58.0
10/2	70	40	8.8	13.4	87.4	66.0
10/3	70	40	8.8	13.4	87.4	66.0
10/4	70	40	11.7	17.4	84.0	56.0
10/5	70	40	11.7	17.4	84.0	56.0
10/9	70	40	9.3	5.2	87.0	87.0
11/9	95	100	18.0	30.0	81.0	70.0
12/12	130	115	19.4	13.0	85.0	89.0

* Received 7 capsules of Holadin, a pancreatic preparation, each day.

NOTE.—Average absorption of protein and fat:
With pancreatin—protein, 70.8; fat, 62.9.
Without pancreatin—protein, 84.7; fat, 73.1.

textbook[2] states that when the external secretion of the pancreas is abolished in the human, a bulky, pale or white stool results, due to excess fat.

We have had several patients in whom the duodenum and part of the head of the pancreas were removed for carcinoma of the ampulla of Vater or head of the pancreas. It is safe to assume that none of these patients had pancreatic juice in their intestine. In one, this was proven at autopsy. They served as excellent subjects for the study of fat absorption in the absence of pancreatic juice (see Tables 2, 3, 4 and Fig. 1). The first case absorbed almost the entire amount of ingested fat. The second patient also absorbed considerable quantities and these became larger in the course of time so that almost normal fat absorption was obtained 4 months after the pancreatectomy. The third patient is alive but apparently requires pancreas by mouth to insure adequate fat digestion. She is gaining weight progressively.

In this connection the work of Dr. Dorothy Andersen on cystic fibrosis of the pancreas in children[1] is significant. In these cases she found complete absence of pancreatic lipase, yet 60% of the ingested fat had been hydrolyzed to fatty acids, suggesting the activity of an intestinal lipase.

TABLE 4.—CASE 3.

A. C. Age, 53. History 392089.
Diagnosis: Carcinoma of the head of the pancreas.
Operation: March 6, 1940. Partial gastrectomy, complete duodenectomy, removal of head and part of body of pancreas, anterior gastroenterostomy, choledocho-enterostomy.
Follow-up: October 8, 1940. Gained about 13 pounds. No obvious metastases. Taking 9 capsules Holadin each day.

DAILY FAT ABSORPTION IN THE ABSENCE OF PANCREATIC JUICE.
(Daily Fat Ingestion, 75 Grams.)

Date, 1940.	Fat in grams contained in 24 hr. stool.	% fat absorption.	Pancreatin.
3/28	63.0	16.0	None
4/2	56.0	25.3	None
6/5	20.8	72.3	9 capsules
6/6	5.7	92.4	9 capsules
6/16	38.0	50.0	None
6/17	40.2	46.4	None
6/18	81.2	0	None

TABLE 5.—CASE 4.

I. A. Age 58. History 591399.
Diagnosis: Carcinoma of the ampulla of Vater.
Operation: December 11, 1939. Resection of the duodenum and part of the head of the pancreas. Gastroenterostomy. Choledocho-enterostomy.
Follow-up: January 21, 1941. Gained about 17 pounds.

DAILY FAT ABSORPTION IN THE ABSENCE OF PANCREATIC JUICE.

Date, 1941.	Grams fat ingested per day.	Grams fat recovered in stool per day.	% fat absorbed.
1/26 1/27 1/28	75	9.77	87

Summary. 1. The glucose assimilation curve in cases of hyperinsulinism due to tumor of the islands of Langerhans is frequently of the diabetic type.

2. Normal glucose tolerance tests were obtained in 3 patients in whom three-quarters of the pancreas had been removed. There was no obvious difficulty with food digestion or absorption.

3. Normal fat absorption is possible when no pancreatic juice enters the intestine.

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VITAMIN C IN THE TREATMENT OF DIABETES.*

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In our studies of possible vitamin deficiencies among diabetic patients, it was thought advisable to investigate vitamin C. The chemical function of vitamin C has been better understood in plant than in animal metabolism. In plants, it is generally agreed that ascorbic acid forms part of a cellular oxidation-reduction system; while most workers agree that in animal tissues glutathione occupies a rôle analogous to ascorbic acid, and that the vitamin has no part in cellular oxidation.[13] Even though there is no proof that vitamin C enters into the cellular oxidation of carbohydrates, various experiments indicate some effect on carbohydrate metabolism in general. Since diabetes is primarily a disturbance of carbohydrate metabolism, which secondarily causes disturbances in metabolism of other foodstuffs as well, any agent which might regulate the handling of carbohydrates assumes great clinical importance.

* This study constitutes a part of the activities supported by the Espy Fund for Research in Diabetes.

In a previous study at the Diabetic Clinic, Cincinnati General Hospital, a survey of 125 diabetic patients was made with respect to their vitamin C status.[9] No relation was found between vitamin C and the diabetic state of the patient. This present paper covers the results of ascorbic acid administration in various dosages to controlled diabetic patients in all states of vitamin C nutrition, in order to observe what effects it may have on subjective complaints and the severity of the disease.

Stepp, Schroeder and Altenburger[12] found that 300 mg. of ascorbic acid given intravenously to 17 patients, both diabetic and otherwise, invariably produced a drop in the blood sugar, in some instances as much as 20% of the starting level. Oshima[7] demonstrated this fall in diabetic individuals only; in normal people the blood sugar remained the same. Guinea-pigs on a C-deficient diet developed a diabetic type of glucose tolerance which was corrected when vitamin C was again added to the diet.[11] Clinically, Pfleger and Scholl[10] and others have found that when ascorbic acid is given orally, the urinary sugar of diabetics is reduced and less insulin is required.

Hirsh[5] administered vitamin C to guinea-pigs and produced an increase in liver glycogen; furthermore, this vitamin offsets the glycogenolytic activity of thyroid extract. Bartelheimer has also stated that glycogen storage in experimental animals is increased after vitamin C.[1] This is of particular interest in relation to diabetes, since many physiologists believe that the primary defect in the diabetic individual is an inability to form and store glycogen. Any agent that promotes glycogenesis and has an action similar to that of insulin might be of practical importance.

Most of the work done on the relation of vitamin C to carbohydrate metabolism has been either to measure the immediate effects of a single intravenous or oral dose, or to follow the effects of vitamin C on diabetics who have come under recent control. One group of workers whose work is widely quoted administered ascorbic acid to a group of uncontrolled diabetics at the same time that a diabetic regimen was started. They disregarded the fact that the tolerance of any diabetic patient improves under treatment, and attributed the beneficial effects to the use of the vitamin. Small laboratory animals have also been used to test the effects of ascorbic acid; but these animals are notoriously prone to show a variety of manifestations, when placed on deficient diets, which would tend to upset their carbohydrate metabolism and make estimation of the results difficult. Since many authors have intimated that vitamin C may be of some practical benefit in the treatment of diabetes mellitus, and since few reports concerning the efficacy of the vitamin appear in the literature, it is the purpose of this paper to discuss the practical benefit actually derived from the administration of various dosages of vitamin C to diabetics over a considerable period of time.

Method of Study. A group of 16 out-patients from the Diabetic Clinic of the Cincinnati General Hospital were taken for this study. Selection was made from those who were willing to coöperate and follow dietary instructions. One colored and 15 white patients were chosen. The average age was 50.8 years, the extremes being 32 and 60 years. All were taking insulin. The observations extended from February to June, 1940.

All of the patients had been controlled in the clinic for 2 to 8 years, with the exception of 2 relatively new patients who had been followed for only 4 and 6 months respectively. They were included since they were quite stable at the time the study was started. It was felt that the selection of these 16 patients eliminated the variable factor of the natural tendency of diabetics to show improvement and decreased insulin requirement early in the period of diabetic control. The length of control was discussed in a previous paper,[8] and its importance cannot be overemphasized.

The diet allowed during the study was the same as had been prescribed for a considerable time previous to the test period. The calories ranged from 1430 to 2300 daily, and the carbohydrate from 100 to 180 gm. Each patient was asked to keep a daily record of all the food eaten, both with respect to type and amount of vegetable, fruit, or meat. The sizes of portions were recorded in common household measurements, and the diets were evaluated first for *dependable* sources of vitamin such as citrus fruits, tomato juice, and raw vegetables, and then for *uncertain* sources such as cooked fruits and vegetables. The table compiled by Bessey[2] was used for estimating the vitamin C content of the various foods. Dependable and uncertain sources were calculated separately and then divided by the number of days the diet was observed, so that the final figures represent the average daily intake from all sources. The theoretical amount of vitamin C that any one diet would allow by proper selection of foods was also calculated, so that two dietary vitamin C figures were available for analysis: 1, the amount that could reasonably be obtained from the diet allowed; 2, the amount actually eaten by the patient.

Before any specific medication was given, a physical examination was made with particular attention to the presence of any signs of scurvy. Examination of the gums and capillary resistance tests were made. Two of the patients had generalized arteriosclerosis with hypertension; 4 had retinitis, and 8 out of the 16 had cataracts, either operated or unoperated. In no case was there a severe infection.

At the beginning of the period, a 1000-mg. 5-hour intravenous saturation test was done. This test was described by Ludden and Wright[6] and was designed to measure the 24-hour output of vitamin C after an intravenous test dose, based on the calculation of the 1½- and 5-hour urinary excretion. Initial blood ascorbic acid level was also measured. The method of Harris was used[4] for the determination of the urine C, and all values were reported in milligrams.

Patients were seen in clinic every 2 to 3 weeks during the time the ascorbic acid was being given. They were weighed at each clinic visit, so that it was possible to follow weight curves during the vitamin administration; and any change in subjective complaints were elicited without the use of leading questions.

Blood sugar determinations were made at the beginning of the study and found to be within reasonable limits. The control of the diabetic state of these patients was observed by examination of the usual 4 daily routine specimens, and by measurement of the blood sugar whenever it was felt necessary. All of the patients remained under good control, as is evidenced by the fact that only 2 showed more than a 2+ sugar during the period of observation. Both instances resulted from glucose ingestion taken to correct mild insulin reaction. The urines of most of the patients were negative except for an occasional trace of sugar after meals, a finding which we consider normal in patients taking protamine insulin. Changes in the

insulin requirement were watched carefully, as this was one of the indices used to measure the effect of the vitamin.

Ascorbic acid tablets were given 3 times a day before meals,* 300, 600, and 1200 mg. being taken daily. The blood levels of ascorbic acid were examined on each clinic visit. No ascorbic acid tablets or foods that contained any appreciable amount of vitamin C were allowed on the morning of blood level determination. The method of Farmer and Apt was used for the blood ascorbic acid level.[3]

Results and Discussion. *Diet Analysis for Vitamin C Content.* Dietary values for carbohydrate, protein, and fat for each patient, theoretical amounts of vitamin C that the diets might reasonably be said to contain, and amounts of C actually eaten by the patients are given in Table 1. If proper selection were made, the dependable sources of vitamin C citrus fruits, tomato juice, and raw vegetables were alone sufficient to cover the daily needs. When the amount

TABLE 1.—ANALYSIS OF CARBOHYDRATE, PROTEIN AND FAT AVAILABLE AND ACTUAL VITAMIN C CONTENT OF DIETS.

	Diet.				Total vitamin C (mg.).			
					Available.*		Actually eaten.	
Patient.	Carbohydrate (gm.).	Proteins (gm.).	Fats (gm.).	Calories.	Dependable.	Uncertain.	Dependable.	Uncertain.
1	165	85	125	2125	100	40	41	57
2	160	70	80	1740	100	40	45	30
3	150	80	100	1820	90	25	0	46
4	150	75	60	1440	90	25	64	61
5	180	80	140	2300	100	40	24	38
6	120	70	115	1795	50	20	80	40
7	130	70	70	1430	50	20	3	20
8	150	75	75	1575	90	25	40	30
9	130	75	85	1585	50	20	80	75
10	160	70	60	1560	100	40	0	19
11	150	80	60	1560	90	25	65	35
12	135	70	100	1700	50	20	0	60
13	160	80	80	1680	100	40	0	25
14	140	60	70	1430	90	25	76	25
15	150	85	140	2190	90	25	40	45
16	100	65	90	1470	50	20	76	35

* Average figures for the common fruits and vegetables.

that is inconstantly present in cooked fruits and vegetables was added, there was a considerable margin of safety. It is entirely possible to design diabetic diets having an adequate amount of vitamin C, if foods with a high natural content of C are chosen. In all but three instances in which the diet was analyzed, the theoretical amount of vitamin the prescribed diet could reasonably contain was higher than the amount eaten. Since all patients received regular instruction about selection of foods, in order that the greatest value per dollar could be obtained, we feel that dietary lack of vitamin C was mainly dependent on likes and dislikes of the patient or improper handling and cooking of foods.

Weight Changes. Of the 16 patients who were on 300 mg. of ascorbic acid daily, 2 lost 5 pounds over a period of 3 weeks, and

* The ascorbic acid for this study was supplied through the courtesy of Parke, Davis & Co.

1 gained 5 pounds over a period of 5 weeks. With the larger doses of 600 and 1200 mg., 1 gained 3 pounds and 1 lost 3. These observations failed to demonstrate any consistent weight change.

The insulin requirement was followed very carefully, because reports in the literature state that the administration of ascorbic acid lessens the insulin need. An effort was made to keep constant all variable factors such as diet, exercise, worry, and infections. During the whole period of observation, only 2 patients needed a significant change in insulin dosage: 1 needed an increase of 8 units, and 1 a decrease of 10. It seems safe to say that ascorbic acid does not consistently alter the insulin requirement in previously well-controlled diabetic patients, as long as their dietary intake remains constant.

Ascorbic acid saturation tests and blood ascorbic acid determinations were made on each patient at the beginning of the period of administration to determine their state of vitamin C nutrition. Although no signs of scurvy were found among any of the patients, 7 of the 16 were found to have fasting blood ascorbic acid values below the so-called scurvy level of 0.4 mg. per 100 cc. Two had levels between 0.4 and 0.8 mg. per 100 cc., and the remaining 7 had levels over 0.8 mg. per 100 cc. A fairly close correlation was found between the blood ascorbic acid level and the milligrams excreted after an intravenous test dose. Of the patients with chemical scurvy, all but 1 had a urinary output of less than 400 mg. after an intravenous test dose of 1000 mg. Of those with blood levels over 0.4 mg. per 100 cc., only 1 failed to excrete less than 400 mg. Since such a close parallel existed between the blood ascorbic acid and the urinary output in the saturation tests, the patients were subsequently followed by measurement of the blood levels alone.

Effect of 300 Mg. Ascorbic Acid on the Blood Levels. In every instance the blood levels rose after the administration of 300 mg. ascorbic acid daily. Whereas a striking increase was found among patients who started with low levels, many of those with a good state of saturation also showed a marked rise. The greatest single increase was found in a patient who started with a blood ascorbic acid of 1 mg. per 100 cc. (Table 2, No. 13). A prolonged accumulative effect from the administration of the vitamin could not be demonstrated. Those who took 300 mg. of ascorbic acid daily for longer than 3 weeks showed lower levels of blood ascorbic acid at the end of the period than those who took it for less than 3 weeks. In observing patients from week to week, the highest levels were found on the first visit after the medication was started; there would then be a slow, progressive fall, even though administration was continued in the same dosage.

The Effect of 600 and 1200 Mg. Ascorbic Acid on the Blood Levels. Ascorbic acid was increased to 600 or 1200 mg. daily immediately after the 300-mg. dosage was discontinued. In spite of the fact that the amount was doubled or quadrupled, no significant changes

could be demonstrated. Six patients showed a rise in blood ascorbic acid levels, 7 showed a drop, and 2 stayed the same. These results indicate that a state of saturation can be reached with a comparatively small dose, and that once it is reached, no further increase in the blood level can be attained. Excretion then matches ingestion.

TABLE 2.—EFFECT OF VARIOUS DOSAGES OF VITAMIN C ON WEIGHT,* INSULIN REQUIREMENT, AND NON-SPECIFIC SYMPTOMS.

Patient.	Sex.	Age.	Weight, pounds.		Insulin, units.		Vitamin C. Saturation test.		Vitamin C. Blood, mg. per 100 cc.		Vitamin C. Daily dosage, mg.	Weeks given.	Non-specific symptoms.
			Beginning.	End.	Beginning.	End.	Blood, mg. per 100 cc.	Total excreted in urine, mg.	Beginning.	End.			
300 MG. DAILY DOSAGE.													
1	F	53	114	115	25	22	0.05	296	0.05	1.11	300	3	+
2	F	41	146	146	30	35	0.15	238	0.15	1.15	300	3	0
3	M	48	130	130	70	70	0.15	377	0.15	1.27	300	4	−
4	M	60	139	139	100	100	0.19	260	0.19	1.07	300	3	0
5	M	58	140	135	35	35	0.22	196	0.22	1.04	300	3	−
6	M	58	139	120	17	17	0.31	413	0.31	1.08	300	5	+
7	F	53	138	136	22	22	0.37	291	0.37	0.98	300	3	0
8	F	56	132	132	40	40	0.48	405	0.48	1.24	300	3	+
9	F	60	126	127	34	34	0.50	760	0.50	1.30	300	7	+
10	M	36	174	169	60	60	0.80	653	0.80	1.22	300	3	+
11	M	40	146	144	30	30	0.81	708	0.81	0.94	300	3	+
12	M	57	115	120	22	22	0.96	712	0.96	1.33	300	5	+
13	F	56	119	117	25	25	1.00	588	1.00	2.56	300	2	+
14	F	58	116	118	16	16	1.00	734	1.00	1.10	300	8	+
15	M	32	124	123	50	50	1.13	372	1.13	1.24	300	3	+
16	F	57	128	130	12	12	1.56	744	1.56	2.15	300	3	+
600 MG. DAILY DOSAGE.													
11	M	40	144	144	30	30			0.94	0.80	600	2	
7	F	53	136	136	22	30			0.98	0.88	600	4	
5	M	58	135	134	35	32			1.04	1.27	600	4	
4	M	60	139	139	100	100			1.07	1.24	600	2	
6	M	58	129	127	17	17			1.08	1.42	600	4	
14	F	58	118	119	16	16			1.10	0.65	600	3	
10	M	35	169	169	60	60			1.22	1.56	600	4	
9	F	60	127	127	34	34			1.30	1.24	600	2	
12	M	57	120	117	22	22			1.33	1.33	600	4	
3	M	48	130	130	70	60			1.37	1.22	600	5	
16	F	57	130	133	12	10			2.15	1.10	600	4	
1200 MG. DAILY DOSAGE.													
2	F	41	146	147	35	38			1.15	1.15	1200	1	
15	M	32	123	123	50	50			1.24	1.68	1200	1	
9	F	60	127	126	34	34			1.24	1.15	1200	1	
8	F	56	132	134	40	40			1.24	1.68	1200	2	

* For diet see Table 1.

Analysis of Subjective Complaints. Since there were no signs of ascorbic acid deficiency, only subjective indices of a general nature could be measured. Nine patients felt better after taking the medication, 5 felt the same, and 2 felt worse. Of the 9 that felt better, 1 who had cataracts noticed an improvement in vision; the remaining 8 noticed an increase in body strength and endurance. It was felt that this improvement had nothing to do with the specific medication, because the greatest improvement was found among those who started with a good state of vitamin C nutrition. Among those patients with chemical scurvy in whom the greatest improvement could be expected, 2 felt better, 3 noticed no change, and 2 felt worse after taking ascorbic acid.

In spite of the fact that there is experimental evidence to show that ascorbic acid has a beneficial effect on the ability of the normal and diabetic individual to metabolize glucose and store glycogen, no practical benefit resulted from its administration. We feel that the best way to assure adequate intake of vitamin C in diabetic patients is by instruction in the proper selection of foods having a high natural content. Supplemental additions of ascorbic acid appear to have no beneficial effect on the diabetic state.

Summary. 1. Ascorbic acid was administered in 300, 600 and 1200 mg. daily doses to 16 diabetic patients in various states of vitamin C nutrition. All patients had been under good control, and were kept as stable as possible during the period of observation.

2. No constant objective improvement resulted from the ascorbic acid administration in any dosage or for any length of time. There was no weight gain or significant change in the insulin requirement. The disease severity remained unchanged.

3. Some subjective improvement, consisting of increased strength and endurance, was found in 9 of the 16, but the least improvement was found among those who started with a poor state of vitamin C nutrition.

4. Regardless of the initial state of vitamin C nutrition, ascorbic acid administration has no effect on the severity of the diabetic state.

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SOME EFFECTS OF IRON ON HEMOGLOBIN FORMATION.

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Although the efficacy of simple iron salts in the treatment of iron deficiency hypochromic anemias is well recognized there are

many unsolved problems in regard to their utilization and mode of action. A more rapid increase in the blood hemoglobin has been noted with the use of excessive amounts of iron than with smaller but apparently adequate amounts. The reason for this has not been satisfactorily explained. Balance studies have shown that a large amount of the administered iron is retained by the body, but in spite of this large retention only a small percentage is utilized immediately in hemoglobin formation, so that a sufficient amount of iron should remain in the tissues for continued hemoglobin increase if this iron is in a utilizable form.[2,3] One might expect, therefore, a continuing rise in the blood hemoglobin after iron therapy has been discontinued, but it is well recognized that in many cases of iron deficiency anemia it is necessary to continue iron medication indefinitely in order to maintain the hemoglobin at its normal level, even though all apparent causes for the anemia have been removed. This maintenance dose of iron need not be as large as that necessary to bring the hemoglobin up to the normal level but must be administered continuously or intermittently for indefinite periods.

During previous balance studies it was found that when 1 gm. of iron and ammonium citrates was administered per day 26.6% of the elemental iron was retained, but only 9.3% was utilized in hemoglobin formation.[3] This means that an average of approximately 37 mg. of iron per day was being stored and we have shown that this storage continues over a long period of time. Where, and in what form, this iron is stored in the body was not determined, but if it is in a utilizable form it should provide adequate iron for continued hemoglobin formation.

This same amount of iron and ammonium citrates, 1 gm. per day, was administered to a group of 12 individuals for a period of 60 days. The subjects for this study were young adults, students and nurses at the University Hospitals, who were healthy except for the mild anemia which was detected on routine examination. None was included who had had a recent hemorrhage, infection, or other illness to account for the anemia. The blood hemoglobin varied from 8.68 to 11.78 gm. per 100 cc., the hematocrit values ranged from 34 to 44%, and the erythrocyte counts from 3,670,000 to 4,800,000 per c.mm. Hemoglobin determinations were done by the Newcomer method,[6] adequately checked by oxygen capacity; the hematocrit values were determined by the Van Allen method,[7] and the erythrocyte counts were done with instruments certified by the United States Bureau of Standards. Each of these determinations was done at approximately 2-week intervals.

Following the administration of iron and ammonium citrates for 60 days the medication was discontinued, but the observations on the blood were continued at the same intervals for periods up to 26 weeks. Some of the subjects stopped reporting for the blood examinations after varying periods of time, as can be seen in the table, so that the averages computed for the later periods are

determined from a smaller number of cases. In the table the averages of the initial blood findings for each group of cases are recorded together with the subsequent average hemoglobin value and the number of patients from which each average is derived. The average hemoglobin gain at 2-week intervals is shown graphically in the charts.

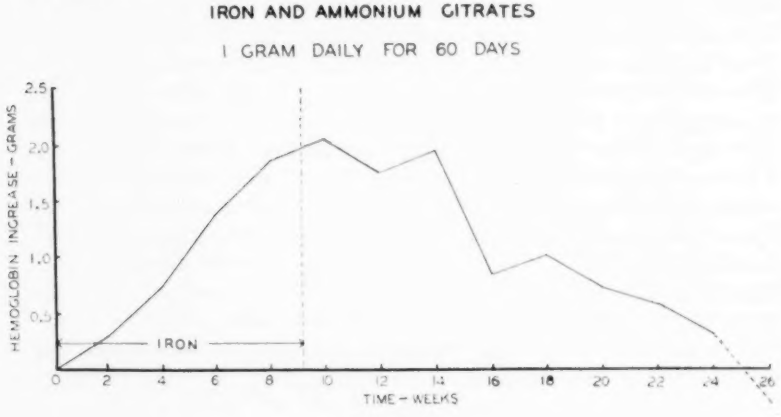

CHART I.

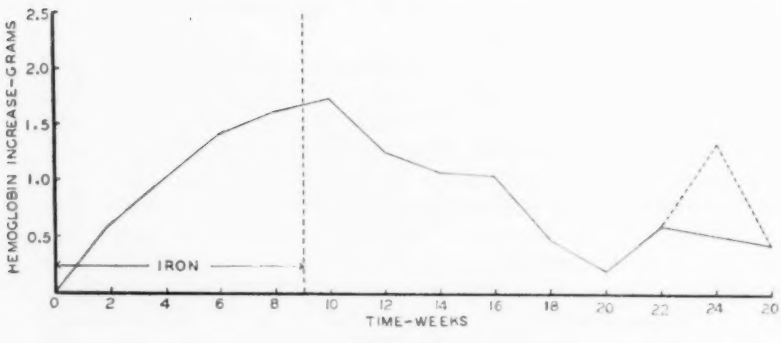

CHART II.

As may be seen in Chart I, there was a gradual increase in the blood hemoglobin during the period of iron administration and continuing for a short period thereafter, so that the peak of hemoglobin regeneration occurred at the 10th week even though iron therapy was discontinued after the 60th day. Following this there was a gradual decrease in the blood hemoglobin, so that the average values had returned to approximately the pre-treatment level by the 26th week.

A similar study was carried out on a group of 13 cases who received 1 gm. of reduced iron per day for 60 days. This preparation contains a higher percentage of metallic iron than do iron and ammonium citrates but it is in a more insoluble form. The blood hemoglobin in this group ranged from 8.68 to 10.94 gm. per 100 cc. with an average value of 10.17 gm. for the entire group. The hematocrits ranged from 33 to 43% and the erythrocyte counts from 3,860,000 to 4,590,000. The procedures were the same as with the preceding group and the hemoglobin response was almost identical as is shown in Chart II. The hemoglobin gradually increased to reach its peak in the 10th week, and then fell to the pre-treatment level after 26 weeks.

In spite of the fact that balance studies had shown a retention of sufficient iron to provide for future hemoglobin regeneration, it would seem logical to explain this fall in hemoglobin to the discontinuation of iron therapy. However, two other groups of subjects with similar hemoglobin levels were followed in the same manner but were given iron continuously throughout the period of observation. To one group was given 1 gm. of iron and ammonium citrates per day and to the other 1 gm. of reduced iron. The average blood hemoglobin level for the 15 individuals receiving iron and ammonium citrates was 11.53 gm. It will be noted in Chart III that the same type of response occurred as in those receiving iron for only 60 days, the peak in the hemoglobin regeneration coming on the 12th week and following this there was a gradual fall. The hemoglobin did not quite drop to the pre-treatment reading, as the average hemoglobin for the group leveled off at a point representing a gain of 0.9 gm. In 7 subjects (average hemoglobin 11.36 gm.) who were given reduced iron the hemoglobin response was practically the same with the peak at 10 weeks followed by a decline to a level which was nearly that which obtained before treatment (Chart IV).

The similarity of the hemoglobin curves in those subjects receiving iron for 60 days and in those receiving iron continuously is striking. In both cases the peak in hemoglobin regeneration occurred in the 10th or 12th week and was followed by a steady regression in the blood hemoglobin to near the pre-treatment level. The rate of regression was nearly the same in both instances. That this uniform fall in hemoglobin is not an artefact produced by charting average values is seen by following hemoglobin levels in individual cases and is the type of response reported by Widdowson and McCance following iron therapy.[9]

In following the results in individual cases it is found that two distinct types of response are obtained. In both types there is the same initial hemoglobin increase but in one group, which includes a majority of the subjects, the hemoglobin subsequently falls to the pre-treatment level. In a second smaller group of cases the hemoglobin drops after the initial rise but remains from 1 to 2 gm. above

the pre-treatment level. Both types of curves occurred in subjects receiving treatment for 60 days as well as in those receiving iron continuously, although in the latter group the persistent increase tended to be higher. No prediction could be made from the original hemoglobin level as to which type of response would occur in a given case since certain cases showing a persistent elevation had original

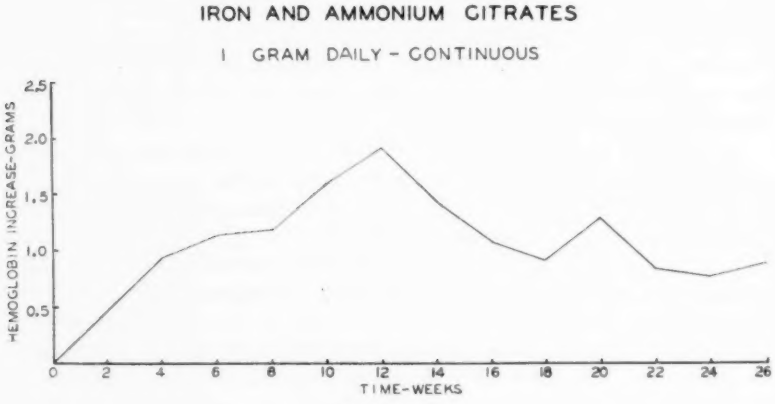

CHART III.

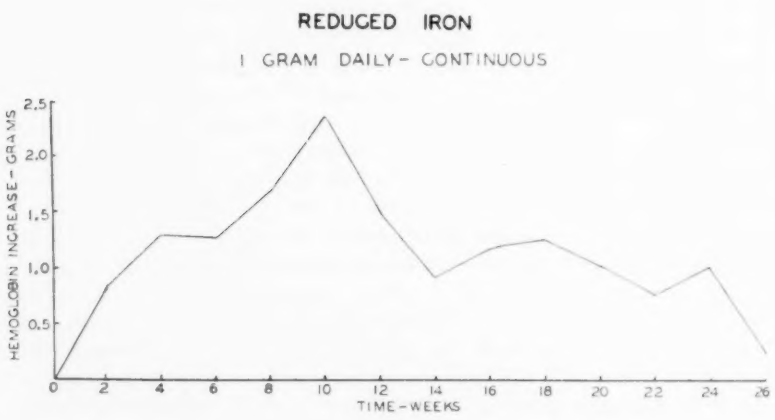

CHART IV.

blood hemoglobins as high as other cases in which the hemoglobin fell to the pre-treatment level. In spite of this fact one is tempted to classify those with a persistent elevation as cases of mild anemia and those in which the hemoglobin fell to the pre-treatment level as cases whose hemoglobin is in a low normal group. Such a classification is used in Charts V and VI which depict the types of curves mentioned for the two groups of cases. This interpretation presupposes that

each individual has a hemoglobin level which is normal for him or herself, but that this normal varies from one individual to another so that a reading which is normal for one individual may represent a mild degree of anemia in another. Such a view is in keeping with the numerous, apparently low, hemoglobin readings which we have

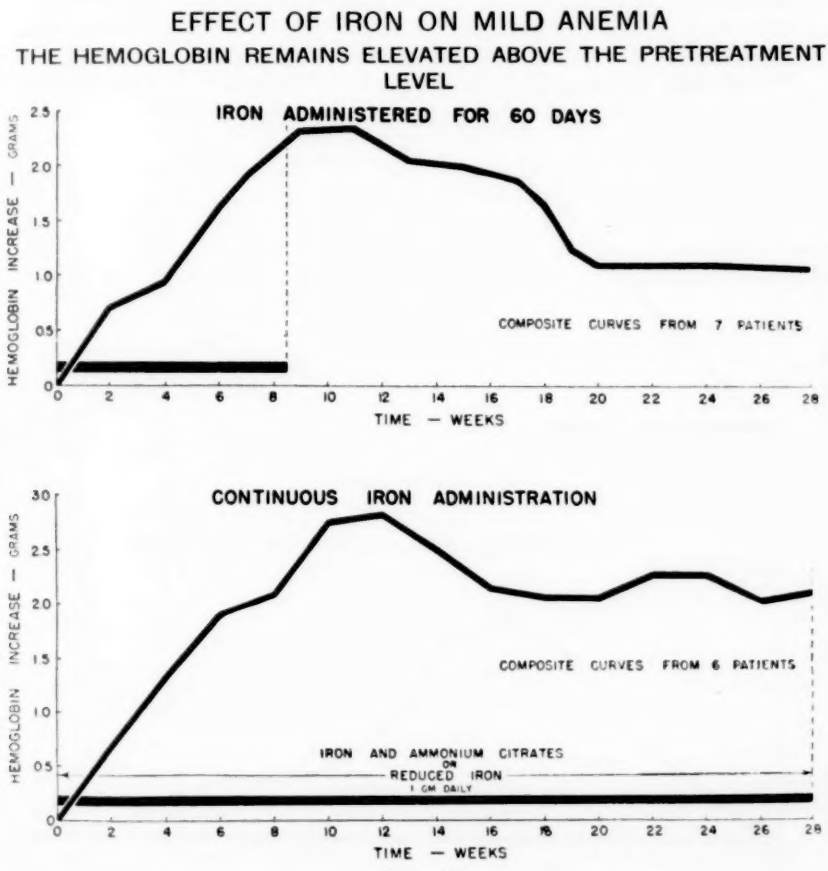
EFFECT OF IRON ON MILD ANEMIA
THE HEMOGLOBIN REMAINS ELEVATED ABOVE THE PRETREATMENT LEVEL
IRON ADMINISTERED FOR 60 DAYS
HEMOGLOBIN INCREASE — GRAMS
COMPOSITE CURVES FROM 7 PATIENTS
TIME — WEEKS
CONTINUOUS IRON ADMINISTRATION
HEMOGLOBIN INCREASE — GRAMS
COMPOSITE CURVES FROM 6 PATIENTS
IRON AND AMMONIUM CITRATES
OR
REDUCED IRON
1 GM DAILY
TIME — WEEKS

CHART V.

Smoothed composite curves from averages of selected cases. Upper curve from Cases 4, 6, 7, 9 and 12 in Group I and Cases 9 and 10 from Group II. The first group received iron and ammonium citrates and the second group reduced iron, 1 gm. per day. Lower curve from Cases 5, 6, 13 and 15 in Group III, and Cases 2 and 6 in Group IV.

encountered in otherwise healthy individuals and also provides the most logical explanation for the variation in the response to iron therapy. If this is true, many patients heretofore considered to have a mild anemia in reality have hemoglobin values which are normal for them. Many hemoglobin values which we have placed in the

low normal group are considerably below the usually accepted normal values.

The most striking feature in these curves is the decrease in hemoglobin after an initial rise and the fact that it occurs regardless of whether or not iron medication is given continuously and regardless of the final hemoglobin level. This suggests that iron is not acting

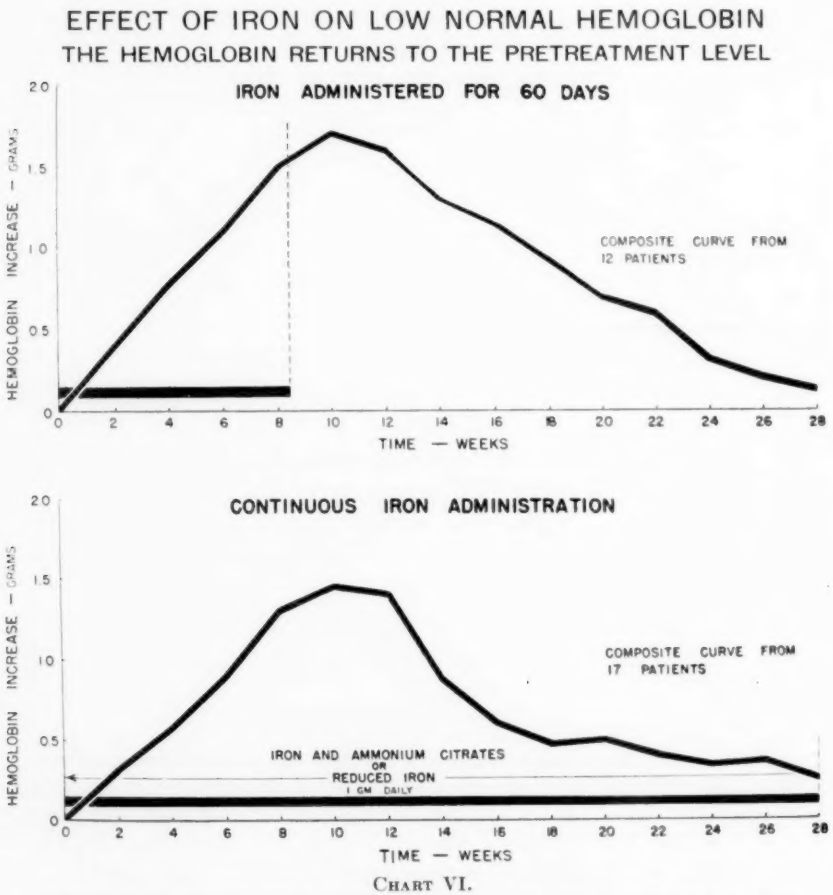
EFFECT OF IRON ON LOW NORMAL HEMOGLOBIN
THE HEMOGLOBIN RETURNS TO THE PRETREATMENT LEVEL
IRON ADMINISTERED FOR 60 DAYS
HEMOGLOBIN INCREASE — GRAMS
TIME — WEEKS
COMPOSITE CURVE FROM 12 PATIENTS
CONTINUOUS IRON ADMINISTRATION
COMPOSITE CURVE FROM 17 PATIENTS
IRON AND AMMONIUM CITRATES OR REDUCED IRON 1 GM DAILY

CHART VI.

Smoothed composite curves from the averages of all cases in the four groups not included in Chart V.

entirely as a form of replacement therapy but that it has an additional stimulating effect. This is evidenced by the fact that the hemoglobin falls from its peak in spite of the continued administration of iron and that even in those individuals showing a permanent elevation there is a preceding peak and regression. The dosage of iron employed was relatively small as compared to the usually

recommended dose of iron salts but is sufficient to supply an overabundance of iron for hemoglobin formation as well as an additional amount for storage. It is known that large amounts of iron cause a more rapid hemoglobin regeneration than do smaller amounts, but the reason for this greater response has not been adequately explained except by supposing a "salt" or catalytic effect.[8] Moore[5] has demonstrated an increase in the blood serum iron after iron therapy and has shown that the increase is greater with larger doses of iron. Experiments with radioactive iron salts have apparently demonstrated the presence of this radioactive iron in the erythrocytes within a few hours.[1,4] It seems probable from these experiments that the iron is taken directly from the blood stream and with

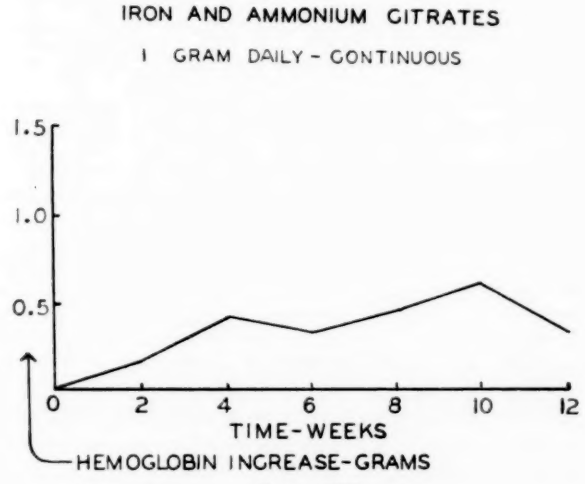

CHART VII.

a larger amount of iron available, hemoglobin is formed more easily and more rapidly, so that the greater response to larger doses is merely due to the availability of larger amounts of iron. This is not the entire picture, however, since the serum iron curves drop rapidly to normal after a few hours and we have shown that the hemoglobin continues its rapid response for 10 to 14 days after iron medication has been discontinued. We do not feel that the changes in the blood serum iron can explain all of the features.

If iron has a stimulating effect on hemoglobin formation in addition to its action as replacement therapy, there should be a response in individuals whose blood hemoglobin levels are relatively high. To test this, a group of 12 male subjects with hemoglobin values ranging from 13.33 to 15.74 gm. per 100 cc. were given 1 gm. of iron and ammonium citrates per day. The hemoglobin response in this group was not great, but the average values for the entire group

show an increase, and the contour of the plotted curve is similar to that obtained in subjects with lower blood hemoglobin values although the changes are less extensive (Chart VII). There is a variation in the individual responses but the average response corresponds so closely to the previous curves that we feel it is of significance as evidence of mild stimulation.

Group.	Medication.			Control.				
		Daily dosage, gm.	Duration.	No. subjects.	Av. R.B.C.	Av. hemat., %	Hemoglobin.	
							Av., gm.	Range, gm.
I	Iron and ammonium citrates	1	60 days	12	4.18	38	10.32	8.68–11.78
II	Reduced iron	1	60 days	13	4.28	37	10.17	8.68–10.94
III	Iron and ammonium citrates	1	Continuous	15	4.81	41	11.53	10.22–14.38
IV	Reduced iron	1	Continuous	7	5.19	42	11.36	8.45–13.75
V	Iron and ammonium citrates	1	Continuous	12	..	46	14.17	13.33–15.74

	2 weeks.		4 weeks.		6 weeks.		8 weeks.		10 weeks.		12 weeks.		14 weeks.	
	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.
Group I	10	10.60	10	11.05	11	11.73	11	12.17	8	12.39	7	12.15	4	12.20
Group II	11	10.76	10	11.19	13	11.60	10	11.74	10	11.85	6	11.69	9	11.29
Group III	14	12.02	14	12.51	14	12.77	10	12.70	9	12.67	15	13.36	9	12.69
Group IV	6	12.08	7	12.64	5	13.07	3	12.04	4	13.13	5	13.19	4	12.57
Group V	10	14.40	6	14.72	8	14.60	6	14.92	6	14.94	6	14.53	..	..

	16 weeks.		18 weeks.		20 weeks.		22 weeks.		24 weeks.		26 weeks.	
	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.	No. subjects.	Av. Hb., gm.
Group I	8	11.52	6	11.02	7	10.95	3	10.81	2	10.94	1	10.52
Group II	6	11.11	2	11.05	3	10.65	3	11.01	2	10.79	1	11.36
Group III	12	12.57	10	12.44	9	12.44	9	11.76	7	11.74	6	11.78
Group IV	5	12.17	4	12.01	4	12.27	4	11.47	3	11.78	1	10.94
Group V	..	..	..	..	..	..	..	..	..	..	..	..

The original detailed tables have been condensed to the present form to conserve space.

Summary and Conclusions. Iron and ammonium citrates and reduced iron produce an increase in the blood hemoglobin which reaches a peak at the end of 10 to 12 weeks. Following this peak there is a gradual reduction in the hemoglobin level regardless of

whether or not the iron is given for a period of 60 days or continuously throughout the period of observation.

The increase in hemoglobin, the peak, and subsequent reduction are similar in patients with mild grades of anemia and in individuals with low normal hemoglobins, although in the latter group the hemoglobin falls to the pre-treatment level, whereas in the former it remains elevated but at a level below the point of maximum response.

A similar but less marked hemoglobin response is obtained in subjects with high hemoglobin values.

These results suggest a stimulating action of iron on hemoglobin formation in addition to its action as replacement therapy.

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THE QUESTION OF "CHRONIC APPENDICITIS."*

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A man 27 years old, possessed of much too fine sensibilities, presented himself as a patient 15 years ago. Except for this one personality defect he was extremely fortunate in birth and all the circumstances of life. He mentioned an occasional sick headache which he took for granted. The complaints for which he sought medical aid related to digestion—gas on stomach with some eructations, feeling of epigastric pressure after meals, intractable constipation, and vomiting on arising on an average of 3 mornings a week. These symptoms began at age 15 in boarding school, and in varying grades of severity had been present ever since, except for one period of 18 months. This was when he was in the army.

This patient passed a splendid physical examination, and in the laboratory nothing abnormal was found, not even a gastric hyperacidity. The gastro-intestinal Roentgen ray studies showed no abnormality in the stomach or small intestine. This additional note was made, "The appendix is seen. It is retrocecal, drains poorly, and shows some evidence of adhesions near the tip. There is some retention after 96 hours, following catharsis. It is believed to be pathologic. The ascending colon is redundant and the cecum

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is low, but shows no evidence of adhesions. There is moderate colonic stasis, a large portion of the barium being retained at 72 hours."

Treatment consisted of suggestions as to diet and an attitude toward life, belladonna, bromides, and the cautious use of cathartics. Recovery was prompt and complete, but not lasting. Six months later, following the illness of his wife with eclampsia, all symptoms returned. The stools at this time, obtained with difficulty, were hard scybala covered with mucus. When assured of the complete recovery of his wife, the same therapeutic measures which had been employed on earlier attacks were promptly effective. Two years later toward the end of his wife's next pregnancy, an attack recurred which lasted until the delivery, without episode, of a normal full-term infant. There was now 60 acidity per cent free acid in the fasting stomach contents, and the stools were entirely characteristic of mucous colitis. Severe, though not disastrous, financial reverses during the first "depression," the death of his mother and lingering fatal illness of his father-in-law, were taken in stride with but minor upsets easily controlled.

Five years ago this patient's case was studied at another hospital. The findings were essentially the same as ours on his original examination 10 years before. An appendectomy was advised and carried out following which the patient took 2 months' vacation. He and his family were delighted that all his symptoms were relieved. Six months later he returned to my office with the old symptoms which he had had for the preceding 2 weeks. The enforced vacation after what he accepted as an unavoidable operation, had given him an "out" from his personal responsibilities; the way the army period presumably had done. His responsibilities were no greater than those incidental to normal living but he carried them very laboriously. Much advice about learning to live quietly in his environment, some belladonna, and enough bromides, relieved again. This was 5 years ago. He is now 42 years old and doing better, but still having attacks.

This is a characteristic case. Repeated disappointments after appendectomy in similar ones led to further study of the problem.

Three series of 100 consecutive cases on the ward, and 2 similar series in the office were questioned particularly about earlier appendectomies. If a patient reported an attack sudden in onset with prompt removal of the appendix, the case was regarded as acute. The case was classified as "chronic" if the appendix had been removed only after a diagnostic survey. Patients in the chronic group were then asked for what symptoms the operation had been done, if relief resulted, and a note was made on the present diagnosis.

Forty-four appendectomies were recorded for the 300 ward patients (14.6%). Twenty of these were acute, 16 were removed as routine during pelvic operations, and 8 were classified as "chronic."

Of ward patients, 2.6% had been operated upon for so-called chronic appendicitis from 2 to 37 years before.

Fifty appendectomies were recorded for the 200 private patients (25%). Thirty-five of these were acute, 6 were removed as routine at other abdominal operations, and 12 were classified as "chronic," the operation performed from one-fourth to 25 years ago. Six per cent of private patients had been operated upon for so-called chronic appendicitis.

It is believed this series of patients is long enough to have some statistical value. Broken down into consecutive series of 100 the percentages for each approach each other closely. The 14.6% of ward patients who had appendectomies, 2.6% of which were for so-called chronic appendicitis, is to be compared with 25% of private patients who had had appendectomies, 6% of which were chronic. This comparison in itself may have significance. Particularly one might note that operation for chronic appendicitis in this series was recorded more than twice as often in the histories of private patients as in those of ward patients.

Two of the 8 ward patients in the chronic appendectomy series were permanently relieved, one of frequent attacks of nausea and another of abdominal pain. This latter might have been acute appendicitis. The remaining 6 ward patients all operated upon for digestive disorders or other abdominal symptoms denied relief following the appendectomy. The present diagnoses on these patients were ureteral colic, tabetic crisis, pulmonary tuberculosis, thyrotoxicosis, cardiovascular-renal disease, and recurrent rheumatic fever. Note the definite diagnosis possible in these 6 ward patients, to be compared later to those made in the 12 private patients.

One of the 12 private patients was a boy 8 years old who, 3 months before, had lost his appendix because of a fever of 6 months' duration, although he had never had an attack of appendicitis. The fever persisted, a possible but not proven case of undulant fever. Another was a man 48 years old who had had the operation 8 years earlier for migraine, without relief. The remaining 10 of the 12 private patients submitted to appendectomy for digestive disorders. Not one was relieved. The indigestion had persisted for from 4 to 25 years after the operation. It is this group of patients I wish to emphasize.

There was a total of 20 cases in the two series, 2 of which, both ward patients, claimed relief; and 6 of which, all ward patients, although not relieved, could be given definite objective diagnoses. Two only of the 10 private patients, operated upon for relief of digestive disorders could be given a definite diagnosis at the time of the present study. A woman 58 years old, 24 years after, and a man 52 years old, 9 years after the appendectomy were shown to have duodenal ulcers. Examination of the remaining 8 developed no objective diagnosis. Neurasthenia, psychasthenia, pylorospasm,

all functional, nervous indigestion if you like, was the best we could do for them.

Discussion. The uniformity of trend of these statistics is surprising. They conform closely, also, to the findings in a similar study of many more patients reported recently by Alvarez.[1]

A single attack of acute appendicitis, perhaps so mild as to go unrecognized, can result in adhesions and other local deformities capable of setting up reflex disturbances of the delicately balanced motor mechanism of the upper and lower gastro-intestinal tract. Repeated disappointment with results of appendectomies in such cases, incorrectly called chronic appendicitis, and the statistics just mentioned indicate, however, that this occurs much less frequently than supposed. The scars of healed acute appendicitis as a cause of indigestion is a diagnosis made—or one might say indulged in—much too often. The hoped-for relief of indigestion after appendectomy would be realized more often if this classification were limited to those cases with a recent history of one or more attacks of what might have been an acute appendicitis, and with local signs in the region of the appendix when the symptoms of indigestion are present. These cases are not, of course, examples of chronic appendicitis. They are patients with low-grade recurrent attacks of acute appendicitis. It would seem that we might well return to our earlier conception taught by the pathologists, that true chronic appendicitis is very rare, if indeed it ever occurs. I have been unable to find an unqualified statement in any treatise on pathologic anatomy by a recognized authority that any lesions are encountered which can properly be called "chronic appendicitis."

The patient with disturbed digestion on a functional basis—old-fashioned nervous indigestion—can have, indeed are more likely than others to have, acute appendicitis. One must be careful not to miss such an attack. Each of our patients with nervous indigestion who had an attack of acute appendicitis obtained relief from the digestive disorders after the appendectomy for periods up to 1 year. Not one of these patients obtained permanent relief, all reacting exactly as those submitting to operation for chronic appendicitis.

Was Henry Thoreau a wise man or a weak one? From a life in Concord in 1845 incomparably less complex than that of today in a big city, he avoided a functional neurosis—possibly it might have had gastro-intestinal manifestations—by an escape. He refused to bear the burden of a conflict, made a choice at the right time, and abided by it as long as was necessary. Toward the end of this excellent course of treatment, planned by himself, he wrote, "Most men are in a strange uncertainty about life . . . . many . . . . propose to creep down the road, pushing . . . . It's a fool's life, as they will find when they get to the end of it, if not before."

Would we get more cures in selected cases of indigestion by pre-

scribing a Walden Pond* than by carrying out an appendectomy on cases of suspected "chronic appendicitis"? The suggestions of this statistical study indicates that we would.

REFERENCE.

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DEMONSTRATION THAT IN NORMAL MAN NO RESERVES OF BLOOD ARE MOBILIZED BY EXERCISE, EPINEPHRINE, AND HEMORRHAGE.

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The circulation readily compensates for a sudden increase in the size of the vascular bed in various parts of the body, or for a sudden decrease in blood volume. During exercise the vessels in the muscles dilate, the bloodflow becomes rapid, and the cardiac output increases. Additional blood is shunted from other parts of the body to the muscles to fill the dilated vascular bed. The more rapid circulation of blood already present in the extremities and muscles also causes the cardiac output to increase. A similar set of compensatory phenomena occurs when the body is heated and the vessels of the skin are dilated.

Compensatory reactions also take place when blood is rapidly removed from the body by hemorrhage or pooled in the extremities by venous congestion. Until considerable blood has been removed, the circulation at rest appears to be perfectly normal; the pulse and blood pressure show little change. During this period, either a redistribution of the blood circulating in the body occurs to make up for the blood removed from the general circulation, or new blood is added to the general circulation from blood reservoirs. Barcroft attempted to elucidate this problem by experiments on animals, and in a brilliant series of investigations demonstrated that in the cat and dog there is a reserve of red blood cells stored in the spleen which can be emptied into the general circulation in time of need.[3] He showed that the spleen of the cat and dog contracted during exercise or hemorrhage, and estimated that the contraction of the

* Today a busy motor highway runs sufficiently near to the location of Walden Pond to disturb its one-time serenity by raucous noises and nervous haste. Possibly this development not only illustrates the need for escape, more today than 90 years ago, but also symbolizes the greater difficulty of its accomplishment.

spleen increased the amount of blood in the circulation 6% to 15%.[5] It has been further demonstrated that the large increase in red cell count and hemoglobin that occurred in the normal cat and dog after fright or exercise was abolished by splenectomy.[1,25,35b] Other workers showed that epinephrine likewise caused contraction of the spleen of the dog and increased the erythrocyte count.[16,22,30]

Barcroft's concept of blood reservoirs was taken up with enthusiasm, and many experiments were devised to demonstrate their existence in man. It soon became apparent that the large increases in hematocrit and hemoglobin values found in the cat and dog after light exercise or after epinephrine did not occur in normal human subjects.[14,29,39] By the blood volume methods then in use, it was found that various stimuli, such as exercise, heat, and epinephrine, produced an increase in the total blood volume with little change in hematocrit reading.[14,24,39] As this increase in volume occurred in splenectomized as well as in normal subjects, it was concluded that other organs, such as the liver and subpapillary venous plexus of the skin, must serve as reservoirs for both red cells and plasma.

It is of fundamental importance to know whether in normal subjects there are reserves of red blood cells, or of plasma, or of both, in order (*a*) to understand the adjustments of the circulation during exercise, fever, dehydration and blood loss, and (*b*) to interpret the changes in hematocrit, hemoglobin, and serum protein values that occur in the peripheral blood in acute experiments such as exercise or administration of various drugs. It is obvious that in the presence of a reserve of red blood cells, which could be quickly mobilized and ejected into the blood stream, the hematocrit reading or hemoglobin concentration would be useless as a method for following changes in plasma volume. If there were a reserve of protein or plasma, changes in plasma protein concentration would not necessarily reflect changes in plasma volume, even in acute experiments.

According to the literature, the three most effective stimuli for mobilizing the blood reserves are exercise, epinephrine, and hemorrhage. Therefore, in order to determine whether there are any blood reserves in normal subjects, the plasma volume, hematocrit reading, hemoglobin concentration, and serum protein concentration were determined before, during, and after: 1, exercise; 2, the administration of epinephrine; and 3, the loss of blood.

Method. All samples of blood were drawn without stasis. The plasma volume was measured by the dye method of Gibson and Evans[17] using the photoelectric micro-colorimeter.[18] A 1.6% solution of potassium oxalate was used as the anticoagulant for determining the hematocrit reading.[17] The hemoglobin concentration in grams per 100 cc. was determined by the method of Evelyn.[15] The serum protein concentration was calculated from the specific gravity of the serum as determined by the falling drop method of Kagan.[26] In 2 of the exercise experiments, the falling drop method was checked by the Kjeldahl method.

From the literature, it appears that in order to demonstrate the function

of the spleen as a blood reservoir, one must use either anesthetized or well-trained animals who have rested for some period of time before the experiment. In the experiments with exercise and the administration of epinephrine, laboratory workers who had no fear of the procedure served as subjects. Novocaine was used for local anesthesia. After the subject had rested quietly in bed for at least 30 minutes, a needle was inserted in an antecubital vein, and three samples of blood were taken for control determinations over a period of 15 minutes. When epinephrine was given, the needle was kept open by injecting a small amount of saline and was not removed until the experiment was completed. The needle was removed during the period of exercise.

Experiments. *Effect of Exercise in Normal and Splenectomized Subjects.* Observations were made on 6 normal and 2 splenectomized subjects. H. W. was an otherwise normal male who had had a splenectomy performed in 1918 for a benign tumor of the spleen. N. S. had had a splenectomy in 1927 because of repeated gastric hemorrhages associated with splenomegaly. He had had another hematemesis about 2 months before the experiment, and was slightly anemic.

Under basal conditions the plasma volume, hematocrit, hemoglobin, and serum protein values were first determined with the patient recumbent. As soon as the last sample was taken, exercise was begun on a bicycle ergometer. The normal subjects became exhausted in from 3 to 5 minutes. The splenectomized subjects did less work and did not exercise to the point of exhaustion. After exercise the subjects returned to the horizontal position and samples of blood were taken for determination of dye concentration, hematocrit, hemoglobin and serum protein values.

TABLE 1.—EFFECT OF EXERCISE ON THE HEMATOCRIT, HEMOGLOBIN, AND PROTEIN LEVELS OF NORMAL AND SPLENECTOMIZED SUBJECTS.

Subject.	Diagnosis.	Age (yrs.).	Wt. (kg.)	Basal plasma volume (cc.).	Relation to exercise.	Hematocrit.	Hemoglobin (gm. per 100 cc.).	Serum protein (gm. per 100 cc.).
E. S.	Normal	32	85	2940	Before	44.9	14.7	6.5, 6.2*
					After	51.0	16.8	7.9, 7.7*
W. D.	Normal	31	74	3060	Before	41.9	14.4	5.9, 6.0*
					After	47.6	16.3	7.0, 7.1*
L. H.	Normal	27	77	3970	Before	43.0	14.6	6.3
					After	49.6	16.6	7.4
R. E.	Normal	27	67	2840	Before	41.7	13.4	6.4
					After	46.7	15.1	7.2
M. M.	Normal	24	75	2630	Before	48.3	15.9	6.6
					After	52.8	17.5	7.2
J. G.	Normal	43	72	2900	Before	44.2	14.4	6.3
					After	49.9	16.0	7.3
H. W.	Splenectomy	31	63	2470	Before	44.7	14.7	7.4
					After	47.2	15.3	7.9
N. S.	Splenectomy	22	68	4100	Before	35.7	10.6	6.5
					After	39.7	11.6	7.1

* Protein determinations were done by Kjeldahl method.

The results were similar in the normal and splenectomized subjects (Table 1). The concentration of the dye increased, indicating a decrease in plasma volume; the hematocrit, hemoglobin and serum

protein values increased. The amount that the plasma volume decreased could not be determined from the change in optical density of the dye-colored serum, because the optical density of dye-free serum increased after exercise.[12b] The direction of the change in plasma volume could, however, be determined and it was clear that the plasma volume decreased and that no new plasma was added to the blood stream. If it is assumed that no protein enters or leaves the blood stream during exercise, the decrease in plasma volume can be calculated from the change in protein concentration. By this method the plasma volume decreased 220 to 590 cc. in the 6 normal subjects, and 160 and 340 cc. respectively in the 2 splenectomized subjects.

For a given increase in protein concentration, there was the same increase in hematocrit reading and hemoglobin concentration in both the normal and splenectomized subjects. As the normal subjects did more work, the absolute changes in protein, hematocrit, and hemoglobin were usually greater in the normal than in the splenectomized subjects. From the changes in protein concentration, hematocrit, and hemoglobin, which occurred after exercise, it was not possible to separate the splenectomized from the normal subjects. The data show that in both normal and splenectomized subjects, exercise caused a decrease in plasma volume, and that no demonstrable quantity of red cells was mobilized from the spleen.

Effect of Epinephrine in Normal and Splenectomized Subjects. Four normal and 2 splenectomized subjects were given 1 mg. of epinephrine subcutaneously immediately after the determination of the basal plasma volume, hematocrit, hemoglobin, and serum protein values (Table 2). The results were similar in both normal and splenectomized subjects. H. W. was the same subject referred to in the exercise experiment; M. S. had had a splenectomy in 1927 for thrombocytopenic purpura. Both subjects had been well since the operation. After 5 to 15 minutes, a rise in heart rate and systolic blood pressure occurred. The optical density of the dye-colored serum, hematocrit, hemoglobin, and serum protein levels increased. The amount that the plasma volume decreased cannot be determined from the change in the optical density of the dye-colored serum, because the optical density of the serum at times increased after the injection of epinephrine. The direction of the change in the plasma volume could, however, be determined and it was clear that the plasma volume did not increase, and that no new plasma was added to the blood stream. The slight rise in protein concentration suggested that there was a slight decrease in plasma volume. The changes in protein, hemoglobin, and hematocrit levels were small, but as they were in the same direction in every experiment, they were considered significant. As these changes occurred in both normal and splenectomized subjects, they cannot be attributed to the spleen. It was not possible to distinguish the

splenectomized from the normal subjects on the basis of the changes in protein, hemoglobin, and hematocrit values after the injection of epinephrine.

TABLE 2.—EFFECT OF THE SUBCUTANEOUS ADMINISTRATION OF EPINEPHRINE ON THE HEMATOCRIT, HEMOGLOBIN, AND PROTEIN LEVELS OF NORMAL AND SPLENECTOMIZED SUBJECTS.

(The resting values for hematocrit, hemoglobin and protein levels represent the average of three determinations.)

Subject.	Relation to injection of epinephrine.	Hematocrit reading.	Hemoglobin (gm. per 100 cc.).	Serum protein (gm. per 100 cc.).
E. G.	Before epinephrine	44.7	14.5	6.6
(normal)	5 min. after epinephrine	45.7	14.9	6.7
	10 " " "	46.5	15.2	6.8
	17 " " "	46.7	15.2	6.9
	26 " " "	46.1	15.2	7.0
D. C.	Before epinephrine	44.9	14.6	6.3
(normal)	5 min. after epinephrine	45.7	14.7	6.3
	10 " " "	45.7	14.9	6.7
	16 " " "	45.9	15.0	6.7
	26 " " "	46.6	15.2	6.6
	36 " " "	46.0	15.2	6.7
E. S.	Before epinephrine	42.8	14.2	6.7
(normal)	5 min. after epinephrine	45.0	14.6	6.8
	10 " " "	44.9	14.8	6.9
	21 " " "	44.6	14.9	6.9
	26 " " "	45.4	14.9	7.0
	31 " " "	45.0	14.9	7.0
	41 " " "	45.2	14.7	7.0
R. E.	Before epinephrine	41.8	13.8	6.4
(normal)	5 min. after epinephrine	43.1	14.1	6.5
	10 " " "	43.6	14.3	6.7
	15 " " "	43.5	14.0	6.6
	25 " " "	43.1	14.0	6.7
R. P.	Before epinephrine	43.2	13.6	7.0
(normal)	5 min. after epinephrine	44.9	14.3	7.2
	10 " " "	44.9	14.3	7.2
	15 " " "	44.7	14.0	7.2
	27 " " "	44.7	13.9	7.2
	33 " " "	45.0	13.8	7.1
H. W.	Before epinephrine	45.6	15.4	7.3
(splenectomized)	12 min. after epinephrine	46.4	15.5	7.4
	28 " " "	46.5	15.8	7.5
	31 " " "	47.2	15.8	7.5
	34 " " "	45.8	15.8	7.6
M. S.	Before epinephrine	44.6	14.2	6.8
(splenectomized)	5 min. after epinephrine	45.5	14.5	6.8
	10 " " "	45.7	14.7	7.0
	16 " " "	46.0	14.4	7.0
	26 " " "	45.0	14.2	7.1
	36 " " "	44.7	14.2	6.8

Effect in Normal Subjects of Hemorrhage and Tourniquets. In the dog, hemorrhage has been shown to cause contraction of the spleen, and may even cause a temporary rise in hematocrit reading if the hemorrhage is not too large.[2,7] Reasoning from animal experiments and from teleologic considerations, hemorrhage should also be an effective means in man of mobilizing blood from any available reservoirs. In experiments previously reported,[13] the plasma volume,

hematocrit value, and serum protein concentration of normal subjects were determined before and after the removal of 760 to 1220 cc. of blood. The hematocrit reading showed a steady decrease and at no time was there any evidence of red cells being poured into the circulation. During the first 2 hours after venesection, the plasma volume increased as protein-poor fluid was added to the circulation. There was no evidence of a reserve of plasma which was distinct from the circulating blood.

Blood was pooled in the limbs by applying tourniquets inflated to diastolic pressure to both upper thighs and one upper arm. In some cases sufficient blood was removed from the head and trunk to induce symptoms of collapse. Determination of the plasma volume and hematocrit level showed that in spite of the decreased quantity of blood in the trunk, no demonstrable number of red blood cells were added to the circulation.

Discussion. Although there is an abundance of evidence that the spleen serves as a reservoir of red cells in the dog, cat and horse,[1,5,25,35a,b] there is little evidence that it has such a function in normal man. Dill, Talbott, and Edwards[10] found that exercise caused a similar increase in hematocrit level and protein concentration in both normal and splenectomized subjects. Other workers[32] found an increase in erythrocyte count in splenectomized as well as normal subjects after the administration of epinephrine, and concluded that this increase must be the result of hemoconcentration. After the injection of thorotrast, changes in size of the human spleen may be followed by Roentgen ray. Investigators[34,37] using this technique have demonstrated that in man the injection of epinephrine causes only a slight decrease in the area of the normal spleen. If the spleen is enlarged, however, epinephrine may cause a marked decrease in size.[38]

In the experiments reported here, the normal and splenectomized subjects showed similar changes in hemoglobin, hematocrit, and protein values after exercise and after administration of epinephrine. These changes, therefore, cannot be attributed to the spleen. In animals in which the spleen acts as an important reservoir of red cells, it is easy to distinguish between normal and splenectomized animals by comparing the hematocrit reading and hemoglobin concentration before and after exercise, or the administration of epinephrine. The fact that this method does not distinguish between normal and splenectomized human subjects indicates that in normal man the spleen is not important as a reservoir of red cells.

Experiments in which the carbon monoxide method of determining the blood volume was used have not produced conclusive evidence that the spleen acts as a reservoir of red cells in normal man. Chang and Harrop,[9] measuring the blood volume by the carbon monoxide method, made observations on 6 subjects before and after exercise. In 3 experiments the change in carbon monoxide con-

centration in the blood was so slight that it was within the experimental error; in 3 cases a just appreciable although definite decrease in carbon monoxide concentration was observed. They interpreted this as due to either a slight diffusion of gas into the muscle hemoglobin or to the addition of a small quantity of red cells to the circulation from the spleen or other reserves. Yang and Chang[10] stated later that, in the time that was allowed for mixing, carbon monoxide diffused evenly through blood in the human spleen. It is possible that the slight decrease in carbon monoxide concentration with exercise (indicating a higher blood volume) resulted from diffusion of some of the carbon monoxide into the muscle hemoglobin.

Barcroft,[4] working with the carbon monoxide method and using an adequate rebreathing time, found an increase in blood volume when human subjects were placed in a warm room. He found little change in hemoglobin concentration. Therefore, an increase in both the red cell volume and plasma volume would have had to occur. As the time was too brief for the formation of new red cells, the increase in red cell volume would have had to be due to the addition of red cells to the circulation from some blood reservoir, such as the spleen. Bazett and his coworkers,[6] using the carbon monoxide method, found a decrease in red cell volume when human subjects were changed from a room maintained at a constant warm temperature to a cool room. In view of the evidence presented by Yang and Chang[10] that in man carbon monoxide mixes with the blood of the spleen if an adequate mixing time is allowed, it is difficult to explain these changes in red cell volume as due to release or storage of red cells in the spleen. A possible explanation may be that a greater quantity of carbon monoxide combines with muscle hemoglobin in a warm environment than in a cool environment. To offer a definite answer to this question, it would be necessary to compare the effect of environmental temperature on splenectomized and normal subjects.

It has been shown that in certain animals other than man, the spleen is not an important reservoir of red blood cells. In the guinea-pig and rabbit, as contrasted with the dog, there is only slight contraction of the spleen and relatively little increase in the hematocrit after the administration of epinephrine.[21] The efficiency of the spleen as a storehouse for red blood cells can be correlated with the amount of muscular tissue in the spleen. The spleens of the dog, cat and horse have large amounts of smooth muscle, while the spleens of the rat, rabbit and man are poor in smooth muscle.[23]

Although the evidence indicates that under normal conditions in man the spleen does not serve as an important reservoir of red cells, there is considerable evidence that under certain pathologic conditions in which the spleen is enlarged, it may fulfill this function. This is particularly true in hemolytic jaundice where a marked increase in hematocrit reading and erythrocyte count may occur

after the subcutaneous injection of epinephrine. This effect does not occur after splenectomy.[38]

Using the older dye methods for determining plasma volume, many investigators found an increase in plasma volume rather than a decrease after exercise.[8,36,39] Workers using the dye method with an adequate mixing time have consistently found that the plasma volume decreased after exercise.[19,27] The older dye methods gave an increased plasma volume after any stimulus which caused an increase in the velocity of the circulation, such as epinephrine, breathing of carbon dioxide, and heat.[33,39] Since these changes in plasma volume were not accompanied by corresponding changes in the hematocrit, it was believed that the red cell volume was also increased. Because of the apparent increase in volume after these various stimuli, the total blood volume obtained at rest was designated as the circulating blood volume and the increase in volume after exercise was thought to be the result of the mobilization of blood from various blood reservoirs.

The older dye methods allowed only a short time between the administration of the dye and the withdrawal of the sample of blood for the determination of dye concentration. It has been shown that complete mixing of the dye in the blood stream may not occur in this period of time.[31] Gibson and Evans[17] pointed out that the mixing time in different subjects varied, and that the average mixing time for normal subjects was 7.5 minutes. With a short circulation time the mixing was rapid; as the circulation time increased the mixing time became more prolonged. It thus appears that what was designated as the circulating blood volume was a falsely low volume because of the allowance of inadequate time for complete mixing of the dye throughout the plasma, and that the change after exercise which was designated as release of blood from blood reservoirs, was only a decrease in dye concentration due to more adequate mixing of the dye.

In the use of the carbon monoxide method, similar errors have been made. Douglas[11] pointed out that the period of rebreathing used by Haldane and Smith[20] in their original method was too short and gave a falsely low volume. The striking increase in volume after exercise and heat described by Eppinger and Schürmeyer[14] was probably the result of using too short a period of rebreathing. Chang and Harrop[9] have shown that as long as 15 minutes of rebreathing is required before a constant concentration of carbon monoxide is obtained in the blood.

The evidence seems to indicate that in the normal human subject there is no place in the body where a measurable quantity of blood lies in non-circulating pools or reservoirs. It is true that all blood is not moving at the same speed and that when a dye or carbon monoxide is added to the blood stream, it is first mixed and shows the highest concentration in the parts of the blood stream that are

flowing more rapidly. It is possible that in part the dye mixes slowly because the central portion of the stream in the small vessels moves more rapidly than does the peripheral portion. This is probably not the main factor because the carbon monoxide mixing time is at least as long as the dye mixing time, and the carbon monoxide is carried by the red cells which move in the axial portion of the stream.

As it has been demonstrated that only about 16% of the blood volume as measured by the dye and hematocrit method is present in one upper and both lower limbs,[12a] it is evident that at rest the majority of the blood must be in the abdominal and thoracic cavity. It is also clear that under certain conditions, such as hemorrhage, this blood can be redistributed. It has been pointed out[28] that the portal system, with its two sets of resistances, probably plays a large part in the adjustments which occur when the vascular bed of the muscles is dilated, or when the blood volume is decreased by hemorrhage or loss of fluid. It is probable that in the resting state blood flows slowly through portions of the splanchnic area, and that when blood is needed in other parts of the body, as after hemorrhage, the small vessels contract, diminishing the size of the vascular bed and furnishing more blood for other portions of the circulation. This is a redistribution of the circulating blood and not the addition of non-circulating blood to the vascular bed.

Summary. 1. Exercise caused a decrease in plasma volume and an increase in hematocrit, hemoglobin and serum protein values in both normal and splenectomized subjects. For a given increase in protein concentration, the same increase in hematocrit reading occurred in both normal and splenectomized subjects.

2. Epinephrine produced an increase in hemoglobin, hematocrit, and serum protein levels in both normal and splenectomized subjects.

3. In normal subjects attempts to demonstrate reserves of red cells or of plasma by removing large quantities of blood were unsuccessful. Pooling of blood in the extremities did not cause a demonstrable discharge of red cells into the circulation.

4. A review of the literature shows that technical errors account for the large increases in blood volume which have been described in normal subjects after stimuli, such as epinephrine or exercise, which increase the velocity of the circulation.

5. Although there is an abundance of evidence that the spleen serves as a reservoir of red blood cells in the dog, cat and horse, the evidence presented here indicates that blood reservoirs of this nature do not exist in normal human subjects.

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THE EFFECT OF ARTERIAL AND VENOUS CONSTRICTION INDUCED BY PAREDRINE (p-HYDROXY-α-METHYL-PHENYLETHYLAMINE HYDROBROMIDE) ON THE LUNG CAPACITY AND ITS SUBDIVISIONS.*

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Earlier work from this laboratory[4b,21a,b] has shown that paredrine,[1] a sympathomimetic amine, causes marked constriction of the peripheral arteries and veins, resulting in increased systemic arterial and venous pressures. Data obtained from studies on the effects of paredrine show that the administration of that drug

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induces hypertension which resembles essential hypertension: in both there is generalized arteriolar constriction without changes in skin temperature, oxygen consumption or cardiac minute volume output.[1,4b,15] It has been suggested[29] that the peripheral vasoconstriction of essential hypertension may increase the blood content of the lungs. The question therefore arises as to whether or not this marked widespread vasoconstriction similarly causes redistribution of the circulating blood. In an attempt to gain information on the effect of the administration of paredrine on the pulmonary blood content, we have made measurements of the pulmonary air capacity and its subdivisions; direct measurement of pulmonary blood volume in man is not possible. Information bearing on this point is essential for a complete understanding of the action of this drug if it is to be used therapeutically; its use has already been suggested in conditions in which it is desirable to raise the blood pressure without increasing the cardiac output directly.[3,4b,23] Many of the properties of paredrine are useful for the present study: its vasoconstricting action is prolonged, it does not cause restlessness or other untoward symptoms, and it is not a bronchodilator.

Methods. Five normal subjects were used, ranging in age from 23 to 35. Measurements were made with the subject in supine position, arms at side, with one small pillow beneath the head. The determinations on Subjects 1, 2, 3, and 4 were made several hours after the last meal, and were preceded by a rest period of 20 minutes. Subject 5 was in the basal, postabsorptive state. Paredrine hydrobromide was given orally in solution, and measurements were made at the peak of the pressor action, usually 15 to 45 minutes after administration. The closed circuit method of Christie[10] was used to determine the functional residual air, which, in that author's terminology, is the air contained in the lungs at the end of normal expiration. The bell type spirometer used in these studies had a capacity of 6 liters, and a dead space, including the mouthpiece, of 1270 cc. A carbon dioxide absorber of the type described by Waters[28] containing 475 gm. of Wilson's Soda Lime, 4-8 mesh, was used in the circuit, and the carbon dioxide content of the air at the end of the experiment was less than 0.4%. Approximately 5 liters of oxygen were added to the spirometer at the start of the experiment. Gas analysis was performed in duplicate, using a Haldane apparatus with a burette calibrated to permit the direct determination of nitrogen in concentrations ranging from 27% to 74%. In the calculation of functional residual air a correction of 100 cc. for nitrogen excretion in a 7-minute test period was used in the modified formula proposed by Hurtado *et al.*[20] and the result was corrected to give volume at 37° C. The rate of oxygen consumption and the respiratory minute volume were determined from the graphic record of the respiration. At the conclusion of the determination, reserve and complementary air were determined separately by measurement on the graphic record of excursions from the resting expiratory level after forced expiration and forced inspiration. Vital capacity was determined separately, using a larger spirometer.

Critique of Method. The small volume closed circuit method for determining residual air has been criticized by Lassen and coworkers,[24] and these authors[12] as well as others[17] have suggested methods to overcome these objections. However, Kaltreider, Fray and Hyde[22] concluded that the error in measurements made by Christie's

method was small. The newer methods are much more complicated, involving either addition of gases to a system at a constant rate or taking repeated alveolar air samples. Christie's method is much simpler, involving a minimum of coöperation on the part of the patient, and has been found reasonably accurate by most observers in normal subjects who do not have an unusually high mid-capacity.[11,17,22,24] Even if a small error occurs in the absolute values obtained, it is felt that the comparative data are valid for the purposes of this study.

The correction of 100 cc. for nitrogen excretion is slightly higher than that originally suggested by Christie. Recent studies by Behnke *et al.*[7] and Richards and coworkers[13] of the elimination of nitrogen through the lung during quiet breathing of 100% oxygen show that approximately 220 cc. of nitrogen is eliminated in 7 minutes in an average normal subject. In our experiments, the nitrogen concentration of the expired air at the termination of the test period was usually 40% to 45%; this represents a decrease of slightly less than 50% from the original value of 79%. Since nitrogen excretion is said to obey the usual gas laws, we have used slightly less than half of the value obtained when pure oxygen is breathed. This can be only an average value, since it will vary with the cardiac output and final nitrogen concentration in each subject tested, but variations from the average figure large enough to impair seriously the accuracy of the determination are improbable. It should be noted that errors due to this factor will not impair the validity of the present study, since results obtained before and after the use of a drug are compared.

Results. Doses of paredrine sufficient to cause marked changes in blood pressure produced no significant change in ventilation, oxygen consumption, total pulmonary capacity or any of its subdivisions (Table 1).

Discussion. The relation between changes in blood content of the lungs and variations in their pulmonary air capacity has been appreciated for many years. It has been suggested that changes in pulmonary capacity and its subdivisions resulting from variations in posture are due to redistribution of the blood in the body,[5,8,16] but this concept is still controversial.[18,25] A clear-cut and familiar instance of change in the subdivisions of the pulmonary capacity secondary to increased blood content is afforded by chronic congestive failure.[2] It has also been shown that a very rapid intravenous infusion (*i. e.*, 1500 cc. in 12 minutes) of physiologic saline solution may decrease the vital capacity in man by as much as 30%.[4] Conversely, increased vital capacity due to diminished blood content of the lungs has been produced experimentally in man by measures which promote pooling of blood in the extremities[5,9c] and by venesection.[9a] The subdivisions of the pulmonary capacity in man can therefore be influenced by various measures which appear to depend on a change in the blood content of the lung.

TABLE 1.—THE EFFECT OF PAREDRINE ON LUNG CAPACITY AND ITS SUBDIVISIONS.

No	Date.	Age.	Sex.	Body surface, sq. m.	Dose.	B.P.	O_2 cons., cc./min.	Normal O_2 cons., cc./min.	BMR., %.	Resp. min. vol., liters.	Functional residual air, liters.	Reserve air, liters.	Residual air (12–13), liters.	Vital capacity, liters.	Total capacity (14–15), liters.	Complement air, liters.
1. W. McB.	5/27	28	M	1.81	Cont.	88/60	273	247	+11	8.2	2.3	...	...	3.7		
										9.5	2.2					
	6/3	..	..	..	Cont.	88/60	267	247	+ 8	8.0	2.3	0.56	1.7	3.7	5.4	2.6
										8.0	2.0	..	1.4	..	5.1	
	6/3	..	..	..	40 mg.	120/90	256	247	+ 4	8.4	2.4	0.56	1.8	3.7	5.5	2.6
	6/26	..	..	..	Cont.	88/60	242	247	− 2	7.5	2.2	0.56	1.6	3.7	5.3	2.6
	6/28	..	..	..	40 mg.	120/80	256	247	+ 4	7.5	2.3	0.56	1.7	5.7	5.4	2.6
										8.4	2.2	..	1.7	..	5.4	
2. M. D. A.	5/29	35	M	1.72	Cont.	..	250	235	+ 6	4.8	2.0	0.56	1.4	4.2	5.6	3.5
										5.3	1.9	..	1.3	..	5.5	
	6/4	..	..	..	Cont.	114/68	246	235	+ 5	4.7	1.8	0.56	1.2	4.2	5.4	3.5
										4.6	1.8	..	1.3	..	5.5	
	6/4	..	..	..	40 mg.	150/84	250	235	+ 6	4.6	1.9	0.60	1.3	4.2	5.5	3.6
										4.4	1.9	..	1.3	..	5.5	
3. V. I.	6/16	28	F	1.54	Cont.	124/68	244	197	+24	5.6	2.3	0.84	1.5	3.7	5.2	2.7
										5.4	2.4	..	1.5	..	5.2	
	6/16	..	..	..	Pared. 30 mg.	190/100	248	197	+26	7.7	2.4	0.72	1.7	3.7	5.4	2.7
						..	..	..	..	4.7	2.1	..	1.4	..	5.1	
4. N. Z.	6/20	23	M	1.96	Cont.	108/60	285	267	+ 7	7.5	3.7	1.00	2.7	5.3	8.4	3.8
										7.2	3.5	..	2.5	..	8.2	
	6/20	..	..	..	Pared. 30 mg.	166/100	270	267	+ 1	6.5	3.5	1.00	2.5	5.3	8.2	3.9
						..	..	..	..	7.2	3.3	..	2.3	..	8.0	
5. S. T.	6/27	35	M	1.84	Cont.	104/70	209	251	−19	8.8	2.3	0.76	1.5	3.7	5.2	2.8
										8.0	1.9	..	1.2	..	4.9	
	6/27	..	..	..	30 mg.	138/96	219	251	−13	7.0	2.1	0.64	1.5	3.7	5.2	3.0
										6.2	2.0	..	1.3	..	5.0	
	6/28	..	..	..	40 mg.	156/100	227	251	− 9	11.0	2.1	0.60	1.5	3.7	5.2	2.8
										8.3	2.1	..	1.5	..	5.2	

Experiments in animals also show that the blood content of the lung may be influenced by various measures. Sjöstrand has reviewed this subject and also presents data from his own experiments.[26] He found that many measures, such as excitement, asphyxia, and drugs change the amount of blood which may be found in the lungs of small animals killed suddenly. Drinker, Peabody, and Blumgart[14] found that the lungs of cats are capable of large changes in blood content under experimental conditions, and that these changes are reflected in changes in respiration.

Only a small number of studies on the effect of sympathomimetic drugs on the pulmonary subdivisions in man have been recorded. Budelmann[9b] reported that adrenalin decreases the vital capacity. Hurtado and Kaltreider,[19] however, found adrenalin exerts no significant effect on subdivisions of the pulmonary volume in an asthmatic subject studied between attacks, although it produces marked changes during an attack. Sympatol, which resembles paredrine in its pharmacologic action, may increase or decrease vital capacity in normal subjects;[9b] veritol (p-hydroxy-a N-dimethylphenethylamine sulphate), which resembles paredrine even more closely, is said to increase it.[6] The paucity of data on the effect of sympathomimetic drugs, especially in regard to subdivisions of the pulmonary air capacity, other than the vital capacity, makes general conclusions impossible. Nevertheless, it is worthy of emphasis that the only thorough studies of the effects of these substances on all the subdivisions of the lung volume are in agreement: neither the total lung volume nor any of its subdivisions is changed by the action of such drugs.

There is little doubt that changes in the blood content of the lungs may occur in animals and man, and that such changes can determine variations in the respiratory subdivisions. The volume of blood in the capillaries is the important factor in this regard. These vessels make up a great part of the alveolar wall; accordingly changes in the air capacity of the lungs reflect changes in the volume of the pulmonary capillary bed as a whole. The absence of changes in the subdivisions of the pulmonary capacity after administration of paredrine suggests that the capillary blood content of the lung is not markedly influenced by this drug; pulmonary congestion is not produced. The fact that the administration of paredrine causes no change in respiratory dynamics is in harmony with this conclusion. Additional evidence in this regard is afforded by the results of earlier studies from this laboratory.[4b] Stewart[27] called attention to the fact that the amount of blood in the lungs may be calculated if the cardiac output and pulmonary circulation time are known. Since neither of these two measurements changes after the administration of paredrine,[4b] it is clear that no change in pulmonary blood volume occurs either.

Summary and Conclusions. 1. The subdivisions of the pulmonary volume were measured in seven experiments on 5 normal subjects after the administration of paredrine.

2. No significant deviation from the control values occurred.

3. Paredrine therefore does not produce marked changes in the blood content of the capillaries of the lungs.

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THE COMPARATIVE VALUE OF ETHER AND PARALDEHYDE AS AGENTS FOR MEASUREMENT OF THE ARM TO LUNG CIRCULATION TIME IN 50 PATIENTS WITH AND 50 PATIENTS WITHOUT HEART FAILURE.

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Measurement of the circulation time of the blood is acquiring increasing importance as a test in the study of heart failure and other diseases affecting the velocity of blood flow. In practice, the term "circulation time" indicates the time elapsing between

the injection of a drug into one of the peripheral veins and the perception of a sensation produced by the drug at a distant point in the patient's body. The term is further modified by designating the point of injection (usually a vein in the antecubital fossa) and the point of perception. Any condition which slows the velocity of blood flow usually causes prolongation of the circulation time; any condition which increases the velocity of blood flow has the effect of shortening the circulation time. This accounts for the usefulness of the test in heart failure, acute and chronic cardiac compression, venous obstruction, myxedema, and polycythemia vera, in all of which the circulation time tends to be prolonged, and in hyperthyroidism in which the circulation time often is shorter than normal.

In clinical practice, two groups of drugs are employed for estimation of the circulation time. One group has as the point of perception the bronchopulmonary or olfactory epithelium, so that the drug traverses a pathway from an antecubital vein through the systemic veins, the right auricle, the right ventricle, and the pulmonary arteries to the pulmonary capillaries. This is called the arm to lung circulation time, pulmonary circulation time, or right heart time. In cases of heart failure, the arm to lung circulation time is essentially an appraisal of the efficiency of the right ventricle. The drugs commonly used for this measurement are ether and paraldehyde. The end point of the test with ether is the appreciation of the odor of the drug by the patient (subjective end point) or by the operator (objective end point). The end point with paraldehyde is a sharp paroxysm of coughing produced by the irritating effect of the drug on the bronchopulmonary epithelium or appreciation of the odor of the drug on the patient's breath by the operator (objective end points) or perception of the odor of the drug by the patient himself (subjective end point).

The second group of drugs used for measuring the circulation time has as the place of perception some point supplied by the peripheral arteries of the head and neck. The pathway of the drug includes that traversed by the drugs used for determination of the arm to lung circulation time and, in addition, the pulmonary veins, left auricle, left ventricle, and systemic arteries. In this group of drugs are calcium gluconate and magnesium sulphate which produce a sensation of warmth in the throat and tongue, saccharin which gives a sweet taste, decholin which gives a bitter taste, sodium cyanide which causes a gasp when it reaches the carotid sinus, and lobelin which causes coughing when it reaches the carotid sinus. These drugs, therefore, are used variously for the arm to tongue circulation time or arm to carotid sinus circulation time. Other terms describing the measurements obtained with these drugs are the arm to head circulation time and total circulation time. This time normally varies from 9 to 16 seconds. In cases of heart

failure, measurement of the total circulation time affords a means for appraisal of the efficiency of the whole heart and, when considered in relation to the arm to lung circulation time, gives in addition an evaluation of the efficiency of the left ventricle in particular.

The lung to tongue circulation time is computed by subtracting the arm to lung from the arm to tongue circulation time. Its accurate computation is said to be important, particularly in cases of isolated right ventricular failure in which it remains within normal limits of from 5 to 10 seconds, although the arm to tongue and arm to lung circulation times are prolonged.[5]

In the course of performing various circulation tests on patients with heart failure, one of us found[3] that paraldehyde sometimes gave outlandish results for the arm to lung circulation time, and that ether was for the most part a more reliable agent. Our present study had its inception therefore in an occasional casual observation of the apparent inaccuracy of the arm to lung circulation time as measured by means of paraldehyde. Candel[1] and Manchester[4] independently have discussed the value of paraldehyde as a means for determination of the arm to lung time. Both authors found this drug to give results comparable to those obtained with ether in patients with normal circulation times and emphasized the advantage which accrues to the use of paraldehyde instead of ether because of the objectivity of the end point of the former drug. It has been our interest to endeavor to compare the relative accuracy of these two agents for measurement of the arm to lung circulation time in patients with various degrees of congestive heart failure. The arm to lung circulation time has been determined by means of ether and paraldehyde, used separately but almost simultaneously, in 50 patients with congestive heart failure and in 50 other patients without heart failure, who served as controls. In the latter group are included a number of patients having etiologic factors for heart disease but in no case was there demonstrable evidence of heart failure at the time the studies were performed.

Technique.—Estimation of the arm to lung circulation time was made in every case after the patient had been resting in bed for at least ½ hour. At the time of the test the patient was placed in the supine position with the arm used, abducted through an angle of about 45 degrees and in such position that the veins of the antecubital fossa were at or only slightly below the level of the right auricle. A syringe containing a mixture of 5 minims of fresh ether with 10 minims of sterile physiologic salt solution was used first. After entering an antecubital vein with a 19- or 20-gauge needle, about 30 seconds was allowed to elapse after removal of the tourniquet, in order to permit restoration of the flow of venous blood. Then the ether-saline mixture was injected *as rapidly as possible* into the vein. A stop watch was started by an assistant at the beginning of the injection and two measurements were made, using both the objective and subjective end points for ether. An important duty of the assistant or the operator consisted in endeavoring to detect the odor of the drug at the patient's nose. When the patient could no longer detect an odor of ether, 1.4 cc. of fresh

paraldehyde was injected *as rapidly as possible* through the needle, which had remained undisturbed in the vein. Again the stop watch was started at the beginning of the injection, and an attempt was made to record three end points for the reaction to paraldehyde in each case. These end points were the perception of an odor of paraldehyde by the patient, similar perception by the operator, and a paroxysm of coughing. In normal persons the arm to lung time measured with ether has been reported to vary between 3.5 and 8 seconds;[2] with paraldehyde, between 3 and 9.5 seconds.[1] Candel postulated 11 seconds as the upper limit of the normal value for the arm to lung time, measured with paraldehyde.

TABLE 1.—CASES WITHOUT HEART FAILURE.

Case No.	Diagnosis.	Arm to lung circulation time (seconds).* Ether.	Paraldehyde.	Difference (paraldehyde minus ether).
1	Bronchiectasis	8.0	8.4	0.4
2	Hypertension	8.0	9.8	1.8
3	Pneumonia	(S)8.0	8.4	0.4
4	Gastric cancer	(O)7.0	7.0	0.0
5	Hypertension	4.0	7.8	3.8
6	Hypertension	5.0	6.5	1.5
7	Hypertension	6.0	10.0	4.0
8	Arteriosclerosis	(O)5.6	10.8	5.2
9	Cerebral apoplexy	(O)8.4	8.2	−0.2
10	Bronchiectasis	(O)8.0	(O)8.0	0.0
11	Hypertension	5.8	7.8	2.0
12	Banti's syndrome	5.6	5.8	0.2
13	Nephritis	4.8	4.8	0.0
14	Hypertension	(S)6.8	7.0	0.2
15	Hypertension	7.6	8.2	0.6
16	Tuberculosis	9.0	8.4	−0.6
17	Cardiac neurosis	5.0	5.0	0.0
18	Tuberculosis	6.0	6.4	0.4
19	Lung abscess	7.0	7.2	0.2
20	Epilepsy	5.0	6.2	1.2
21	Coronary arteriosclerosis	(O)7.0	9.0	2.0
22	Hypertension	(O)6.0	6.2	0.2
23	Hypertension	(S)7.4	11.0	3.6
24	Hypertension	7.0	9.8	2.8
25	Hypertension	(S)5.4	10.0	4.6
26	Tuberculosis	6.0	6.8	0.8
27	Alcoholism	(O)7.0	7.2	0.2
28	Bronchiectasis	8.2	9.0	0.8
29	Cerebral apoplexy	9.0	9.2	0.2
30	Hypertension	(O)8.4	8.6	0.2
31	Hypertension	(O)9.4	10.0	0.6
32	Hematemesis	(S)7.0	7.4	0.4
33	Brain tumor	(S)6.4	6.8	0.4
34	Tabes dorsalis	8.0	8.4	0.4
35	Hypertension	6.2	7.2	1.0
36	Pleurisy	7.6	7.8	0.2
37	Lung abscess	8.0	8.4	0.4
38	Cerebral vascular syphilis	5.0	5.2	0.2
39	Cirrhosis of liver	(S)7.6	8.0	0.4
40	Rheumatoid arthritis	4.8	5.4	0.6
41	Bronchial asthma	(S)4.0	(S)8.0	4.0
42	Ventricular tachycardia	8.8	10.6	1.8
43	Neurosis	8.6	9.0	0.4
44	Tuberculosis	(S)6.6	6.8	0.2
45	Peptic ulcer	(S)7.4	8.0	0.6
46	Bronchial asthma	7.4	9.4	2.0
47	Bronchiectasis	8.6	9.6	1.0
48	Hypertension	5.0	8.0	3.0
49	Pneumonia	9.0	8.8	−0.2
50	Bronchial asthma	8.0	(O)8.0	0.0

* (O) indicates that the end point of the time recorded was the perception of the odor of the drug by the operator. (S) indicates that the end point was the perception of the odor by the patient. The absence of any indicating letter before the time recorded for ether means that the subjective and objective end points were obtained simultaneously. The absence of any indicating letter before the time recorded for paraldehyde means that the end point was a paroxysm of coughing.

Clinical Results. The results obtained for measurement of the arm to lung circulation times by means of ether and paraldehyde in the 50 control cases are shown in Table 1; those for the 50 cases of heart failure are shown in Table 2. In the tables, the lowest value for the circulation time is the one recorded. For example, in some cases the subjective end point for ether is obtained sooner than the objective end point, and *vice versa*. Similarly, it occasionally happens that the odor of paraldehyde is perceived several

TABLE 2.—CASES WITH HEART FAILURE.

Case No.	Etiologic type of heart disease.	Arm to lung circulation time (seconds).* Ether.	Paraldehyde.	Difference (paraldehyde minus ether).
1	Rheumatic	12.6	16.4	3.8
2	Arteriosclerotic	21.0	28.2	7.2
3	Hypertensive	19.4	29.0	9.6
4	Rheumatic	12.2	21.0	8.8
5	Rheumatic	(O)15.0	18.0	3.0
6	Hypertensive	12.6	25.0	12.4
7	Hypertensive	14.8	18.4	3.6
8	Rheumatic	42.0	No end point	
9	Hypertensive	13.4	9.6	−3.8
10	Hypertensive	9.4	(S)(O)9.4	0.0
11	Hypertensive	(O)17.0	13.0	−4.0
12	Rheumatic	(O) 8.6	15.0	6.4
13	Arteriosclerotic	10.0	13.6	3.6
14	Hypertensive	9.0	11.0	2.0
15	Beriberi	(O)21.0	(S)41.0	20.0
16	Hypertensive	(O)14.6	24.2	9.6
17	Hypertensive	27.0	No end point	
18	Hypertensive	(O) 8.8	15.0	6.2
19	Hypertensive	11.0	8.0	−3.0
20	Syphilitic	22.4	42.6	20.2
21	Hypertensive	11.6	12.4	0.8
22	Arteriosclerotic	(S)13.0	12.0	0.0
23	Syphilitic	32.0	No end point	
24	Syphilitic	17.0	(S)19.0	2.0
25	Arteriosclerotic	10.0	16.8	6.8
26	Hypertensive	14.0	(S)(O)20.0	6.0
27	Hypertensive	10.6	14.4	3.8
28	Hypertensive	11.0	13.0	2.0
29	Hypertensive	20.0	22.0	2.0
30	Hypertensive	(O)10.0	(S)24.0	14.0
31	Arteriosclerotic	(S)11.4	15.0	4.6
32	Hypertensive	(O)14.0	19.4	5.4
33	Arteriosclerotic	16.6	21.4	4.8
34	Hypertensive	11.0	9.6	−1.4
35	Syphilitic	(O)13.0	17.0	4.0
36	Syphilitic	12.0	(S)15.0	2.8
37	Hypertensive	11.0	15.0	4.0
38	Syphilitic	15.0	21.0	6.0
39	Hypertensive	(O)11.0	9.4	−1.6
40	Hypertensive	12.0	10.0	−2.0
41	Hypertensive	(S)20.0	21.0	1.0
42	Hypertensive	(O)11.2	16.0	4.8
43	Rheumatic	(O)15.0	18.0	3.0
44	Syphilitic	(O)10.0	12.0	2.0
45	Rheumatic	15.0	18.0	3.0
46	Syphilitic	11.0	15.2	4.2
47	Hypertensive	(S)10.6	14.8	4.2
48	Hypertensive	(S)11.0	18.0	7.0
49	Hypertensive	(O) 9.0	12.0	3.0
50	Arteriosclerotic	(O)11.0	14.0	3.0

* (O) indicates that the end point of the time recorded was the perception of the odor of the drug by the operator. (S) indicates that the end point was the perception of the odor by the patient. The absence of any indicating letter before the time recorded for ether means that the subjective and objective end points were obtained simultaneously. The absence of any indicating letter before the time recorded for paraldehyde means that the end point was a paroxysm of coughing.

seconds before the patient coughs, although the paroxysm of coughing and the odor of the drug usually appear simultaneously.

In the control cases, there was no instance in which there was complete failure to obtain an end point with ether and paraldehyde. There was 1 case in which the patient had no sense of smell, and the end points for both drugs were objective. There was another case in which the patient did not notice the odor of paraldehyde, and there were 2 cases in which paraldehyde failed to provoke coughing, but in these 3 cases the odor of the drug was easily detected objectively by the operator.

Forty two (84%) of the 50 control cases had a shorter arm to lung circulation time when measured with ether than with paraldehyde. The difference in seconds varied from 0.2 to 5.2. In almost all cases, however, the difference was insignificant for practical purposes. Furthermore, in all cases the circulation time measurements with both drugs were within the limits established as normal by other workers. There were 5 cases (10%) in which the values were identical for the two measurements. In the remaining 3 cases (6%) the values obtained with paraldehyde were shorter by from 0.2 to 0.6 second than those with ether, again an insignificant difference.

Very few unpleasant reactions were noted as the result of administering either ether or paraldehyde to the control cases. In 3 cases, paraldehyde caused slight drowsiness and in 1 case, transient headache. The odor of paraldehyde tended to persist longer than that of ether, and in many cases was objectionable to the patient for as long as 10 minutes. In 1 case, ether caused severe pain along the course of the vein into which it was injected. The pain lasted about 24 hours, but there was no objective evidence of phlebitis.

In the cases of heart failure, there were no instances in which the use of ether for measuring the circulation time was a complete failure. In 2 cases, the patient did not smell the drug, but the operator was able to record its presence. Using paraldehyde, there were 3 cases in which no end point to the reaction could be obtained. In these cases, the circulation time, as measured with ether, was more prolonged than in any others of the group. There were 3 other cases in which paraldehyde failed to induce coughing, although the odor of the drug could be detected either by the patient or by the operator. Thus, there were 6 cases in all in which paraldehyde did not produce coughing. This should serve to emphasize that a paroxysm of coughing is not necessarily the most reliable end point for the reaction with paraldehyde. An attempt should always be made both by the patient and by the operator to obtain the odor of the drug.

There were 39 cases (76%) of heart failure in which the circulation time measured by means of ether was shorter than that measured by means of paraldehyde. The differences of the two measure-

ments ranged from 0.8 to 20.2 seconds, with an average difference of 5.76 seconds. There were 29 cases (58%) in which the difference was greater than 3 seconds and therefore certainly significant. There were 3 additional cases (6%) in which no difference could be computed because an end point was not obtained with paraldehyde. In 2 cases (4%) the circulation time was the same with each drug. In 6 cases (12%) the circulation time with paraldehyde was shorter than that obtained by means of ether. Differences in these cases ranged from 1.4 to 4 seconds and were greater than 3 seconds in only 2 cases.

Unpleasant side reactions with ether and paraldehyde were a little more common in the patients with heart failure than in the control group. Drowsiness after injection of paraldehyde was observed in 7 cases. Again, the odor of paraldehyde was disagreeable in many instances because of the length of time it persisted. In 8 cases, ether provoked transient but objectionable pain.

Discussion. It is obvious from our study that the records obtained for the arm to lung circulation time with paraldehyde are approximately the same as those obtained with ether in subjects who have no cause for slowing of the velocity of blood flow. However, in the majority of cases of heart failure the records obtained with paraldehyde are significantly longer than those obtained with ether. Moreover, the differences in circulation time measured with these two drugs are by no means constant and bear no absolute relation to the duration of the circulation time. These facts indicate that ether is a more reliable agent for accurate measurement of the arm to lung circulation time. It is true that the use of paraldehyde will demonstrate the presence of a slowed circulation rate such as occurs in heart failure. However, paraldehyde gives a less exact appraisal of the severity of heart failure, and probably could not be depended upon for the type of accurate measurements that are occasionally needed in the diagnosis of isolated right ventricular failure, in which a knowledge of the lung to tongue circulation time is of considerable importance.[5]

It is presumed that the reaction produced as an end point by any drug used for measurement of the circulation time depends upon the arrival at the point of perception of an adequate concentration of the drug. Therefore, in any case in which the concentration of the drug is inadequate, no end point for the circulation time can be obtained, or in cases in which the concentration is only partially adequate, a delayed reaction may result. It seems likely that in cases in which the velocity of the circulation is slowed, paraldehyde usually fails to reach the point of perception in sufficient concentration. Possibly, the use of larger doses than those originally recommended for paraldehyde would give more reliable results, but unpleasant side effects probably would be more frequent and more severe. The inferiority of paraldehyde as compared to ether

may have its basis in two factors. Paraldehyde is less volatile and consequently must diffuse more slowly from the pulmonary capillaries into the air passages of the lungs. Further, paraldehyde is less miscible with blood than ether, and consequently would be carried along in the blood stream less rapidly.

Summary and Conclusions. 1. Measurement of the circulation time is useful in the diagnosis and study of a number of diseases, and especially of heart failure.

2. A comparison of the relative value of ether and paraldehyde for measurement of the arm to lung circulation time is presented. These two drugs have already been reported to give approximately equal results in normal persons. This has been confirmed in our studies in 50 patients having no cause for delay of the circulation time.

3. Comparison of circulation time measurements obtained almost simultaneously by means of ether and paraldehyde in each of 50 patients with heart failure show that measurements with paraldehyde are usually significantly longer than those with ether. Such differences constitute an inaccuracy which may be misleading clinically.

4. Speculation as to the possible reasons for the discrepancy in measurements made with ether and paraldehyde is offered, and the conclusion drawn that ether is the agent of choice for estimation of the arm to lung circulation time.

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THE CHARACTERISTIC ELECTROCARDIOGRAMS IN LEFT VENTRICULAR STRAIN WITH AND WITHOUT AXIS DEVIATION.*

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The characteristic alterations in electrocardiograms of patients with primary left ventricular strain have been previously discussed in the literature.[1,2,6,12,13,17,19,22,24] The typical forms with axis deviation are definitely established, but there has been too little discus-

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sion of the incidence and significance of the form without axis deviation. Our attention was directed to the subject because, in the daily observation of routine electrocardiograms, we had noticed several instances in which patients with etiologic causes for an added burden on the left ventricle failed to show the expected electrical deviation. This occurred in some cases even when the classical *S–T–T* deviations in Lead 1, and occasionally in Leads 1 and 2, expected in left ventricular preponderance were present. Some years ago, Cohn[6] drew attention to the fact that an abnormal *T* wave in Lead 1 was more stable than axis deviation under the influence of change in heart position. He, therefore, predicted that future experience might reveal that these T_1 changes would be of greater diagnostic importance than axis deviation. A few years later, Barnes and Whitten[2] pointed out that 20% of patients who present *T* wave negativity in Lead 1 as a sign of left ventricular strain do not show any electrical deviation, from which they concluded that the factors causing axis deviation probably differ from those which determine the *T* wave negativity. In the present report we wish to present the results of a systematic analysis of electrocardiograms taken routinely on patients with lesions which primarily increase the work of the left ventricle. This study was undertaken in order to determine the frequency of appearance of the type of electrocardiogram without axis deviation in such conditions, and to evaluate its possible causes.

The cases used were selected at random from the hospital or clinic files. The greatest percentage of records used were from patients with a sustained arterial hypertension showing at several different sittings a diastolic pressure of 90 mm. Hg or more. The patients with acute infections, such as acute hemorrhagic nephritis, pneumonia and those with thyrotoxicosis were excluded. In addition to the hypertensive group, a number of fully developed syphilitic and rheumatic aortic valvular deformities were included. The history and physical findings of all the cases were carefully reviewed to exclude any cases that might have had a recent or old myocardial infarction, since such a circumstance would complicate the electrocardiographic contour. Furthermore, cases were discarded in which serial tracings cast a suspicion of the presence of a recent myocardial infarction. Finally, all cases with a *QRS* duration of 0.12 second or longer were also excluded, as were those having a history of receiving large amounts of digitalis or an appearance in the electrocardiogram suggesting excessive digitalization.

Of the 178 cases finally selected, 148 were patients with hypertension, with or without arteriosclerosis, 18 had rheumatic and 12 syphilitic aortic valvular involvement. Serial records were obtained on 72 (40%) of these patients. In 24 of the cases, necropsy had been performed. A teleoroentgenogram was available in each of the 178 cases from which to determine the probable heart size. We

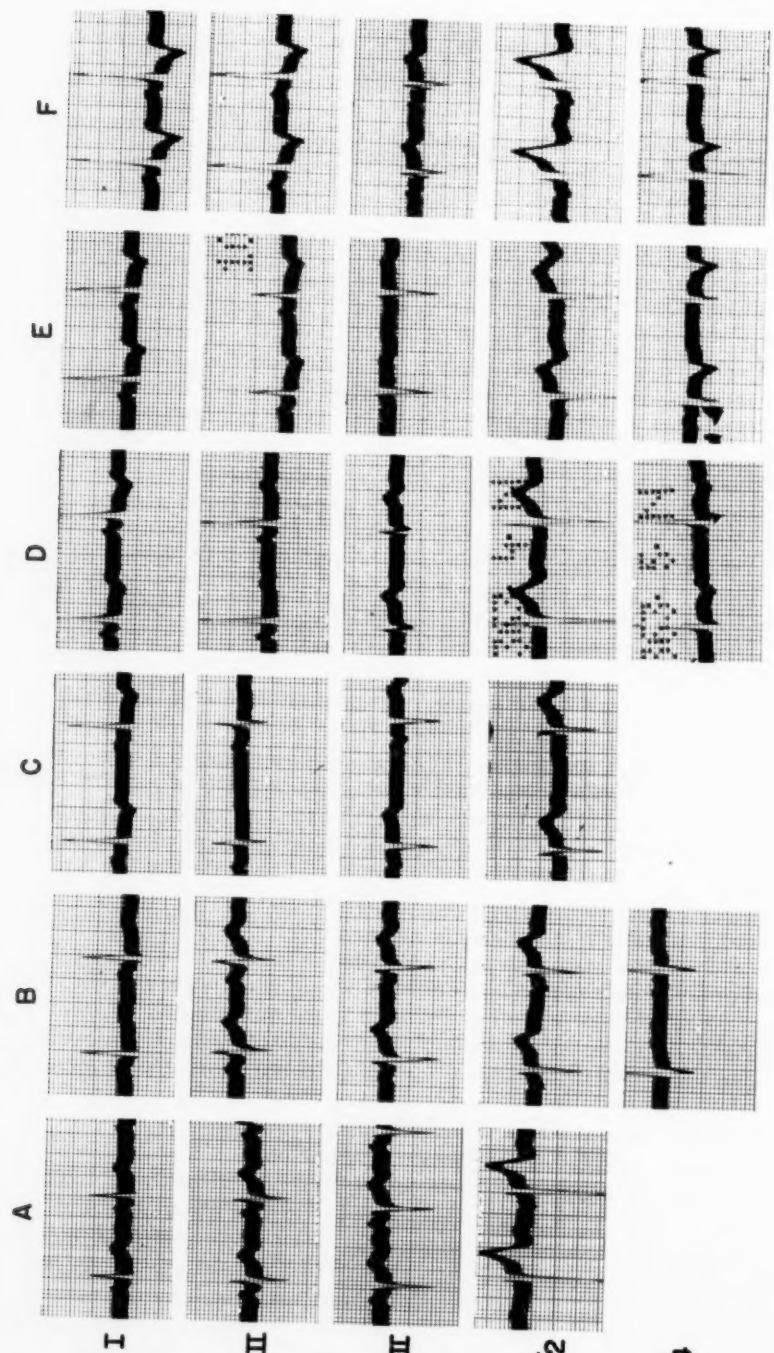

FIG 1.

were able to divide the records in this series into three groups, the first two groups being characterized by axis deviation, one with and the other without the characteristic *S–T–T* changes, and the last, the concordant group, in which the characteristic *S–T–T* alterations were present, but without any axis deviation.

In the first type with axis deviation, the *QRS* complex has its major deflection upright in Lead 1, and inverted in Leads 2 and 3. Furthermore, the *QRS* in Leads 2 and 3 usually have two phases and are of the "S" type, *i. e.*, the final inverted phase is one-quarter or more of the initial upright one. These *QRS* changes are not accompanied by any *T* wave or *S–T* segment abnormalities (Fig. 1, *A*).

In the second type with axis deviation, *QRS* has its major deflection upright in Leads 1 and 2 and *QRS* in Lead 3 is mainly or entirely inverted and of the "S" type. The striking change is in the *S–T–T* segment. In Leads 1 and 3, and occasionally in Lead 2 also, the *S–T–T* segment is deviated in a direction opposite to the major deflection of the *QRS* complex of the lead (Fig. 1, *E* and *F*). Thus *S–T* is depressed and *T* is inverted in Lead 1 (and 2) and *S–T* elevated and *T* upright in Lead 3. It is significant that the convexity of *S–T* is directed upward in Lead 1 (and 2) and downward in Lead 3.

Less advanced and intermediate forms of the two types are also to be found (Fig. 1, *D*) in which some of the features are absent, and mixed types combining the abnormalities of the two foregoing groups are common (Fig. 1, *B* and *C*).

In the group without axis deviation, the concordant group, the major *QRS* deflection is upright in all three leads and the classical *S–T–T* changes described in the second type with axis deviation

LEGEND FOR FIG. 1.

FIG. 1.—Examples of Type 1, Type 2, and the mixed type of left ventricular strain.*

Segment *A*. A young woman of 30 with chronic glomerulonephritis and hypertension (180/120) of many years' duration. It is a typical example of Type 1 as described in the text.

Segment *B*. A man of 65 with arterial hypertension of many years' duration associated with dyspnea on exertion and angina pectoris. It shows a mixed type in that $S–T_1$ is depressed and T_1 is tiny and it has an equiphasic QRS_2.

Segment *C*. A man of 69 with hypertensive and arteriosclerotic heart disease. It shows a more usual mixed type, in that the typical *S–T–T* complex in Lead 1 is directed opposite to the major upright *QRS* deflection and QRS_2 is diphasic and has an *S* wave.

Segment *D*. A woman of 64 who had a marked hypertension (190/120) for at least 2 years associated with symptoms of dyspnea, headaches, and dizziness. It shows the second type of left ventricular strain as described in the text. The *S–T–T* complex in Lead 1 is classical but Lead 2 shows an earlier stage.

Segment *E*. A woman of 50 who had arterial hypertension, averaging 184/110 for many years associated with symptoms of dyspnea on exertion and headaches. It shows another example of Type 2 in which Lead 2 resembles Lead 1.

Segment *F*. A male of 60 who had arteriosclerotic and hypertensive heart disease, with a blood pressure of 190/110 and dyspnea and angina pectoris on exertion, for many years. It shows another example of Type 2 but more advanced than Segment *E*.

* In all instances of this and subsequent records *QRS* is normal in duration, unless otherwise specified.

is found in Lead 1 and occasionally in Lead 2 (Fig. 2). In this series no instance was found in which the major phase of *QRS* was inverted in all the limb leads.

Results. *Frequency of Types.* The greatest number of records seen fell into the second type with axis deviation; 52 cases (29%) were classically of this variety. In 10 of these, the records differed from the classical pattern, in that T_3 was also inverted. The next

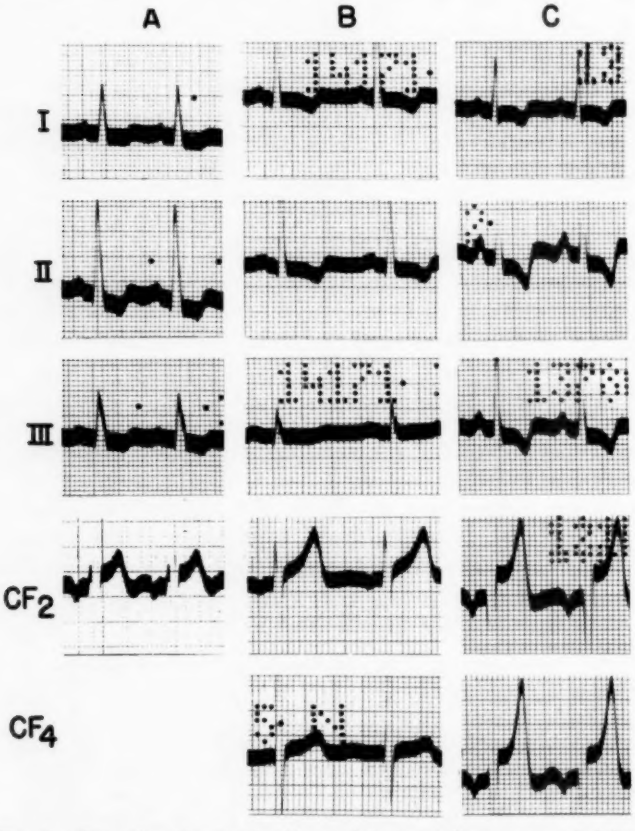

FIG. 2.—Examples of concordant type of electrocardiograms seen in left ventricular strain.

Segment *A*. A male of 51 whose autopsy findings are discussed in the text. It shows an upright *QRS* in all three limb leads and the *S–T–T* complex oppositely directed.

Segment *B*. A male of 65 whose autopsy findings are also discussed in the text. It shows the same type of record as *A* with a more classical *S–T–T* configuration in Leads 1 and 2.

Segment C. A male of 28 with a marked rheumatic aortic stenosis and mitral stenosis and insufficiency without any evidence of congestive heart failure. The findings in the limb leads are classical for this type. Note the entirely inverted *QRS*, the abnormally elevated *S–T* segments, and the abnormally tall *T* waves in the chest leads. These chest lead abnormalities, suggestive of coronary insufficiency, can all be attributed to the left ventricular strain.

most frequent pattern resembled the second type with axis deviation, except that the *T* wave in Lead 1 was small and upright, instead of being inverted (Fig. 3, *B*); at the same time the *S–T* segment was depressed 0.5 to 2 mm. below the isoelectric line in Lead 1, or Leads 1 and 2, and had a downwardly directed convexity. This form, as noted later, is an earlier stage in the evolution of the electrocardiogram to the more classical pattern. There were 38 cases (21%) of this variety.

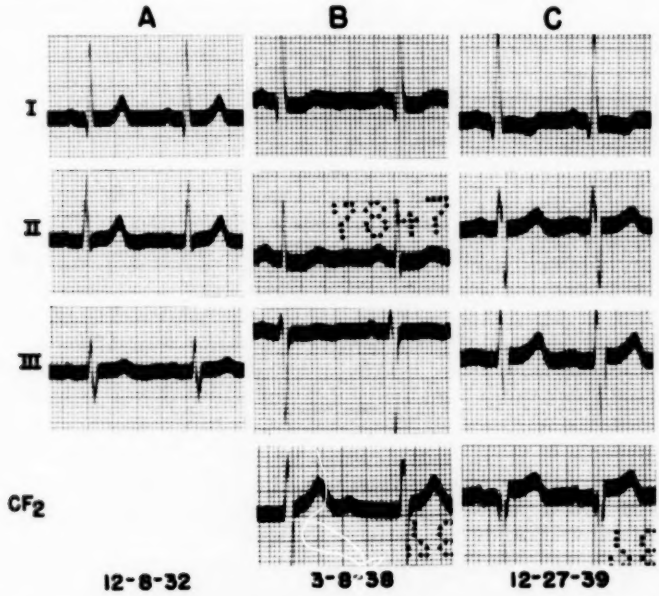

FIG. 3.—Shown to illustrate the progression of the electrocardiographic changes from the second to the mixed type.

This woman of 46 first discovered that she had arterial hypertension in 1932, at which time record *A* was taken. It shows a normal *QRST* complex in all three leads with only a left axis shift (normal) indicated by an *S* wave in Lead 3.

When Segment B was taken in 1938, her blood pressure was 255/150 and she now complained of dyspnea on exertion, headaches and nocturia. It shows depressed *S–T* segments in Leads 1 and 2 and smaller *T* waves in these leads. QRS_2 has become mainly inverted but CF_2 has a normal appearance. This is an early stage of the second type.

One and a half years later, when Segment *C* was taken, the *S–T* in Lead 1 has developed an upward bowing and the *T* wave is now inverted. QRS_2 has now become diphasic, with an *S* wave, and *T* in Leads 2 and 3 are taller. In CF_2, the *QRS* has become entirely inverted and notched, the *S–T* slightly more elevated and the *T* wave smaller. This record is a typical mixed type.

The first type with axis deviation was found in 22 instances (12%). There were 22 records (12%) of the mixed variety with axis deviation; in these the *QRS* pattern was of the first type but the *S–T–T* in Lead 1 (and Lead 2) was of the second type with axis deviation.

There were 17 cases (10%) in which there was no axis deviation

but the typical S–T–T changes were found in Lead 1. In 11 others (6%), the only abnormalities noted in the record were S–T depression in Lead 1, or Leads 1 and 2. A simple left axis shift, in which only QRS_3 was mainly or entirely inverted, but with no abnormalities of the S–T–T complexes in Leads 1 and 2 was seen in 12 (7%) patients (Fig. 3, *A*). In 2 of these T_3 was also inverted. There were 4 records (3%) which could not be classified in the above groups because of the presence of marked low voltage of the ventricular complex in all 3 leads.

The most characteristic feature present throughout the series was the classical S–T–T deviation in Lead 1. This was found in 91 patients (51% of the entire group). There was no axis deviation in 19% of these, which conforms rather closely to the frequency in Barnes and Whitten's series.[2]

Chest Lead Appearance. The configuration of the chest leads in all of the above groups was similar. In CF_2, the lead used most commonly by us, there was a consistent diminution in the height of the initial upward phase of the *QRS* complex (Figs. 1, *A*, *B*, *C* and *F*, and 2, *A*). An initial upward deflection of 3 mm. or less was noted in 77% of the cases. There were 9 records in which *QRS* was entirely inverted (Figs. 1, *E*, and 2, *C*). Occasionally *QRS* was *W* in type or *M* in type. The S–T segment was usually normal and only rarely was it elevated more than 3 mm. (Fig. 2, *C*). The *T* wave was normal in height, except on rare occasions when it was tall (Fig. 2, *C*). *T* wave inversion was noted in 7 instances and in some of these *QRS* was chiefly or entirely upright.

For the past 2 years we have also used the chest lead CF_4 in the routine examination of our patients, but we cannot present definite percentage data as to the commoner types found because our series is too small. In general, it has been our experience that when the heart is definitely enlarged so that the electrode is not at the apex, CF_4 resembles the usual type noted in CF_2 (Figs. 2, *B* and *C*, and 5, *B*). Our observations indicate that when the heart is not greatly enlarged and the chest electrode is near the apex, the *QRS* complex tends to be upright and the S–T–T downwardly directed, an appearance similar to Lead 1 (Figs. 1, *D*, *E* and *F*, and 7).

Necropsy Series. Predominant left ventricular hypertrophy was found in all 24 patients on whom autopsy reports were available. Cases are illustrated in Figures 2, *A*, 2, *B*, and 6. There was no definite correlation noted between the heart weight and the electrocardiographic appearance. In the 7 cases that had an inversion of T_1, the smallest heart weighed 350 gm., the largest 540 (average heart weight, 450 gm.). A similar distribution was noted in those patients with the first type of electrocardiogram with axis deviation and the average heart weight was approximately the same. The largest heart in this whole series weighed 850 gm. and showed a normal left axis shift (QRS_3 inverted) and a diminution in the

height of the T waves in the limb leads. All of the hearts showed varying degrees of coronary sclerosis and myocardial fibrosis, but there were none with evidence of old or recent myocardial infarction. The average age of the patients in the autopsy series was 60 years.

Correlation with Roentgen Ray Heart Size. There was a similar lack of correlation of electrocardiographic appearance and heart size as judged by the Roentgen ray silhouette. Our series discloses that the various types of electrocardiographic patterns enumerated above can be found with relatively small hearts as well as with grossly enlarged ones. In the appraisal of cardiac size by the teleoroentgenogram, we used cardiac configuration and the simplest cardiac measurements, *i. e.*, the ratio

$$\frac{\text{greatest transverse diameter of the heart}}{\text{greatest transverse diameter of the thorax at the level of the left diaphragm}}.$$

We realize that with such a simple cardiothoracic measurement, minor degrees of cardiac hypertrophy will not be evident, but with an evaluation of contour and physical findings, a reasonable degree of accuracy is possible. Hodges[7] has stated that due to the diverse physical stature of individuals, no procedure of recording heart size is infallible and that fluoroscopic examination is the best control. We have arbitrarily accepted a cardiothoracic ratio of 50% or more (in the adult) as evidence of a larger than normal heart. Seventy-seven per cent of the entire series had a cardiothoracic ratio of 50% or more, although it was noted that 92% of the patients with T_1 negativity showed enlarged hearts. The group that showed the greatest percentage of grossly enlarged hearts (60% of the chest diameter or more) was the concordant group. It was seen in 62.5% of these cases.

Changes in Serial Electrocardiograms. In reviewing the cases that had many records over a period of years, it was noted that there was a characteristic progression in the development of the classical types. The earliest change usually noted was an axis deviation with the record still within normal limits (Fig. 3). Later a depression of the S–T segment in Leads 1 and 2 developed. Associated with this, there was a decrease in the amplitude of the T wave in these leads (Fig. 3). At this stage, the depressed S–T segment is concave upward. In the later progression, which may not appear for several years, the S–T assumes a convex upward curve in Lead 1 (and 2) and the T wave in these leads becomes at first diphasic, and later inverted with asymmetrical limbs. This progression caused several cases starting as a Type 1 with axis deviation to change to a mixed type. This progression in cases of the second type with axis deviation shows the steps by which the classical form is attained. In addition to the S–T–T evolution, QRS alterations are sometimes seen in Type 2 so that QRS_2 tends to become of the "S" type, resulting in this way in the appearance of the

mixed type. In several instances it was observed that a record normal at the start may develop into the concordant type without axis deviation (Fig. 4), or into Type 1, Type 2 or the mixed type with axis deviation. Occasionally, a Type 2 with axis deviation was seen to lose its axis deviation and conform to the concordant type without axis deviation (Fig. 6). Viewing our entire experience, we are impressed that the progressive changes of the *S–T–T* deviations in Lead 1 to the classical pattern is the most characteristic feature in the electrocardiograms of patients with protracted

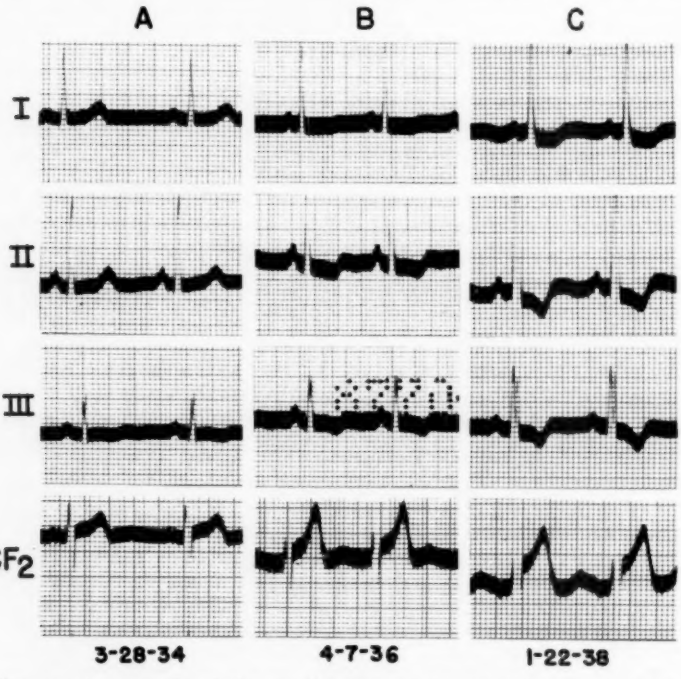

FIG. 4.—An example of the development of the concordant type of left ventricular strain.

This patient, a female of 41, had had a marked arterial hypertension since 1934 and since then had had several episodes of congestive heart failure from which she recovered. Segment *A* is a record probably within normal limits. Segment *B*, taken 2 years later, shows *S–T* depressions and *T*-wave inversions in all three leads. In addition, the initial upward phase of QRS_4 has diminished in amplitude, the *S–T* segment has become slightly more elevated and the *T* wave taller. Segment *C* is similar to Segment *B* except that the *T* waves have become deeper and $S–T_4$ more elevated. The progressive nature of the changes, their late development and their persistence, as shown here, are characteristic of left ventricular strain.

left ventricular strain (Figs. 3 and 4). The long period involved in its evolution, and its persistence, once it has developed, distinguishes the left ventricular strain electrocardiogram from that seen in myocardial infarction, even aside from the difference in their detailed contour when fully developed (Figs. 5 and 6).

Concordant Type of Left Ventricular Strain. In the 17 patients who presented the classical *S–T–T* deviation of left ventricular strain in Lead 1, without showing any electrical axis deviation, 11 cases had hypertensive cardiovascular disease and 9 of these had had at least one episode of congestive heart failure. In 4 others, chronic rheumatic aortic valvular disease with an associated mitral stenosis and insufficiency was present and in 2 patients syphilitic aortic

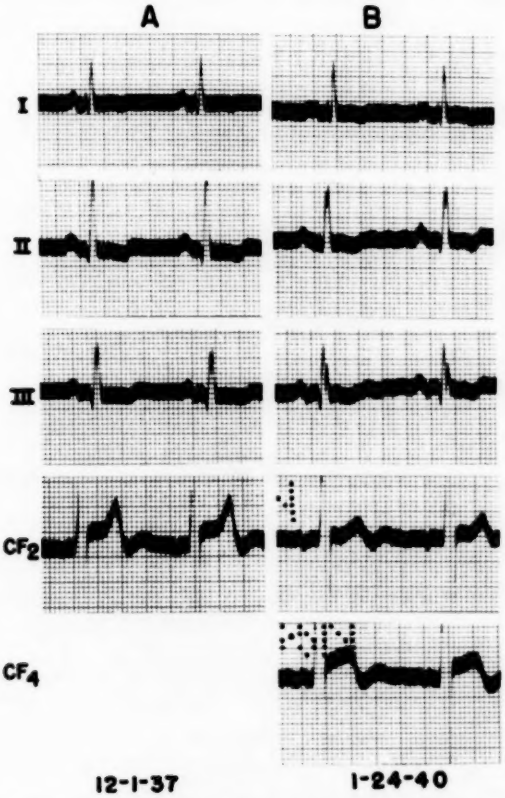

FIG. 5.—Illustrates the persistence of the electrocardiographic changes, once they have appeared, in an instance of the concordant type of left ventricular strain.

The patient, a male, of 52, had a free syphilitic aortic regurgitation and had been in congestive cardiac failure on many occasions. Segment *A*, taken in 1937, shows the absence of axis deviation and the *S–T–T* complexes directed oppositely to the *QRS* in all three leads. CF_2 is normal in appearance. A record, Segment *B*, taken 3 years later, shows a pattern almost identical with Segment *A*, except that T_4 is smaller. CF_4 is normal in configuration.

insufficiency (Fig. 5) was the cause. In both of the latter, congestive heart failure was also present.

Three of the above patients, with the concordant type of left ventricular strain, were examined at necropsy. One of these, who

had hypertension for many years and had been in congestive failure several times, revealed a markedly enlarged heart, weighing 625 gm., involving chiefly the left ventricle but also the right ventricle to a moderate degree. In addition, there was a moderate degree of coronary sclerosis and myocardial fibrosis, without myocardial infarction (Fig. 6). The second patient, who had been afflicted with allergic bronchial asthma since childhood and had developed arterial hypertension in his later years, was seen in the hospital in terminal congestive failure. Necropsy showed a tremendously enlarged heart, weighing 830 gm., with both left and right ventricles involved.

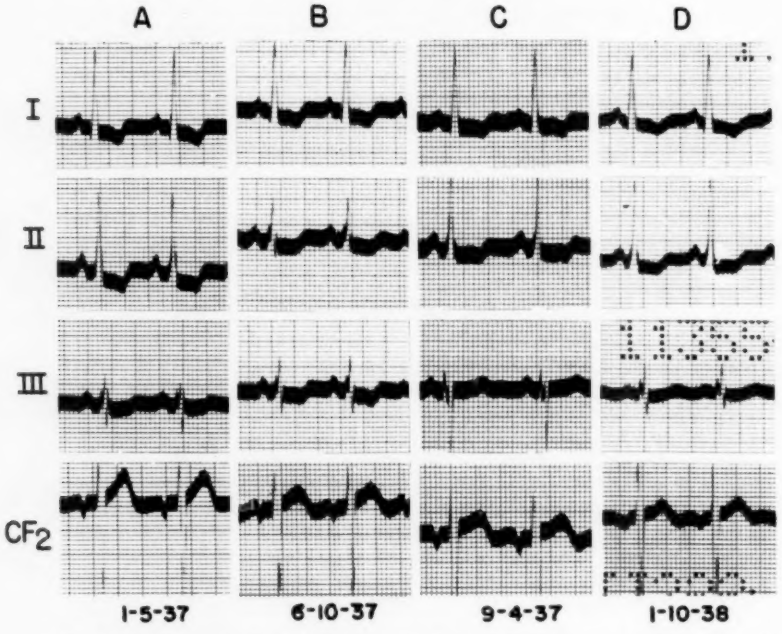

FIG. 6.—These records, taken over a period of 1½ years on a male of 61, with hypertensive cardiovascular renal disease (whose autopsy findings are discussed in the text) shows the characteristic *S–T–T* deviations in Leads 1 and 2 found in left ventricular strain. The change in axis from an inverted QRS_3 (as in Segments *A* and *C*) to a mainly upright QRS_3 (as in Segments *B* and *D*) without any material change in Leads 1 and 2 during these periods, is again illustrative of the comparative diagnostic value of the *S–T–T* changes as contrasted with axis deviation. It will also be noted that CF_2 has undergone very little alteration during this time, retaining its normal appearance except for the inverted P_4. In this instance no evidence of a recent or old myocardial infarction was found proving that left ventricular strain can cause this contour.

There was no coronary occlusion nor myocardial infarct, but a moderate amount of coronary sclerosis and myocardial fibrosis was present. Arteriolar nephrosclerosis, bilateral hydrothoraces and emphysema were also present (Fig. 2, *A*). The third patient, who also had hypertension for many years, died in the hospital of an

unrelated cause. At necropsy, the heart weighed 450 gm. and there was left ventricular hypertrophy and a normal right ventricle. A massive left hydrothorax, with displacement of the heart to the right, noted previously in the Roentgen ray examination, was found to be due to a pleural fibrosarcoma. A moderate amount of coronary sclerosis was present (Fig. 2, *B*).

Inversion of the *T* wave in all three limb leads was found in 8 of the 17 patients of the concordant group (Figs. 2, *A*, 2, *C*, 4, *C*, 5 and 6, *B*). Four of these patients were in the hypertensive group, 2 in the rheumatic and 2 in the syphilitic aortic valvular group. In 2 instances of the concordant series, in which serial records were taken over a period of years, progressive changes were noted, culminating in the classical *S–T–T* deviation in Lead 1, but no axis deviation was noted at any time (Fig. 4). Both of these patients had arterial hypertension, one with a history of frank congestive failure, the other only with symptoms of dyspnea on exertion.

Discussion. It is thus to be noted that the most constant feature of the electrocardiograms in primary left ventricular strain is the classical *S–T* deviation occurring in Lead 1. A progressive evolution of the *S–T–T* segment to this stage was seen occurring in cases which at first had a normal left axis shift, in those which started with the first type of left ventricular strain with axis deviation, and even in those which were first observed without any axis deviation. Although axis deviation is found in the majority of the cases, and is a major sign of preponderant hypertrophy, we have found that in about one-fifth of the cases no electrical axis deviation may be seen.

Our analysis suggests that the absence of electrical axis deviation is due to the neutralizing effect of either a concomitant right ventricular hypertrophy or of a change in the position of the heart. The effect of position change is shown clearly in Figure 7, in which a respiratory change in the position of the heart causes QRS_3 to become upright in two beats, and at the same time T_3 to become inverted and $S–T_3$ depressed. This change shows how easily the concordant type could be caused by a lasting change in the heart's position. The fact that the commonest causes of right ventricular hypertrophy is a preceding left ventricular hypertrophy,[21] a fact now well established, would suggest that this mechanism would be an important one for the occurrence of an electrocardiogram with left ventricular strain without axis deviation. In our series, this was the probable factor in the majority of our cases. Hypertension, syphilitic aortic insufficiency and rheumatic aortic valve involvement all can lead to this. The frequent presence of an associated mitral valve deformity makes the combination of right and left ventricular hypertrophy more common in rheumatic aortic valvular disease. The superposition of right ventricular strain in patients with left ventricular strain may come about because of associated lesions such as chronic pulmonary disease[20] or chest deformity which

increase the pulmonary arterial pressure. The existence of such concomitant factors which tend to nullify the electrical deviation in left ventricular preponderance must be fully recognized. In these cases in which the primary strain on the left heart ultimately causes strain on the right heart, the condition of absent axis deviation may be a sign of advanced stage of strain.

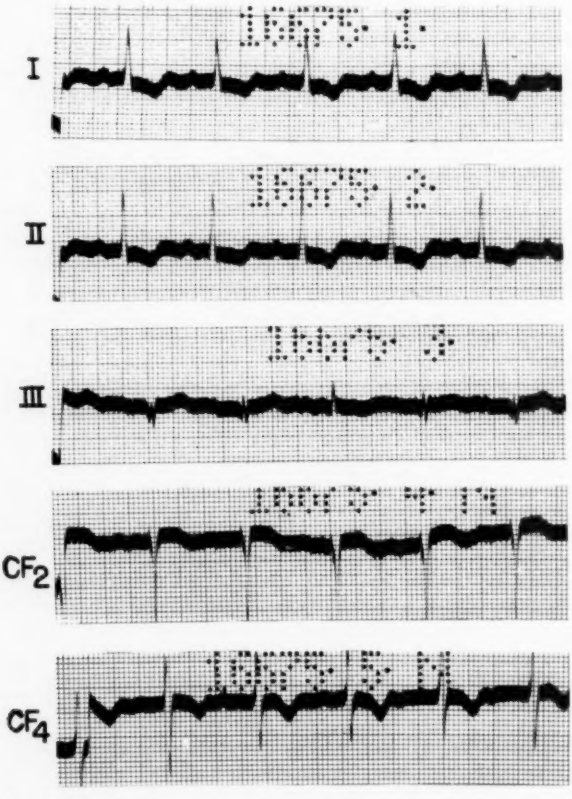

FIG. 7.—Shows the effect of respiratory changes in position of the heart in neutralizing axis deviation from a woman of 52, with arterial hypertension (160/120). It will be seen, in Lead 3, that the *QRS* changes gradually from an entirely inverted complex to an upright one with opposite deviation of the *S–T–T* complex. The *S–T–T* in Leads 1 and 2 undergoes only slight changes during comparable periods, as does QRS_3. Such respiratory changes, although of greater degree than usually present, again show the comparative value of the *S–T–T* changes in Lead 1. It also shows how readily the second type of left ventricular strain can shift to the concordant type.

Apparently, those factors nullifying axis deviation, do not affect the *S–T–T* changes as readily. Thus the *S–T–T* changes may remain as the sole diagnostic clue of the presence of a long-standing and severe left ventricular strain. This experience of ours therefore

lends further evidence to Cohn's belief[6] that the T wave changes are as important as axis deviation and to Barnes'[1] assertion that absence of axis deviation does not minimize the significance of T wave inversion in Lead 1.

The full-blown changes present in Lead 1 in left ventricular strain must not be confused with those instances of T_1 inversion due to numerous other causes. Katz[8a] has presented a critical survey of the various causes of T wave negativity. The most commonly mistaken diagnosis is that of a recent myocardial infarction of the anterior wall. The use of serial records in cases of confusion will show the characteristic evolution of the major electrocardiographic changes in infarction.[3b] It is a pertinent feature of records denoting left ventricular strain that the changes are slow in their evolution and more or less permanent once they have appeared.[13,19] It is, however, true that on occasion a T_1 inversion due to chronic coronary insufficiency may persist unchanged.[3a] This factor of persistence of abnormalities may also be used to differentiate those cases of T_1 negativity occurring in acute nephritis[11,15] and in acute infectious diseases.[14] A perusal of the clinical history and findings will help to clarify the diagnosis in cases of doubt. One important drug that occasionally may mimic the S–T–T changes is digitalis.[4,8b] Digitalis most commonly produces a depression of the S–T interval but this depression consists of a flattening of the S–T which makes this segment merge imperceptibly with the T wave, instead of the depressed S–T having an upward convexity separating it clearly from the inverted T wave as seen in left ventricular strain. In the intermediate stages of digitalis deformity, confusion may arise but the withdrawal of the drug will permit an evaluation, although several weeks may be required before the digitalis effect wears off. The chest leads are seldom of much assistance.

It can be readily appreciated that left ventricular strain is not the only etiologic agent for T_1 negativity or for the special S–T–T combination, nor is it our intention to imply this, but it is a major factor in persistent cases and should be so recognized after dismissing other possibilities.

The classical S–T–T deviation in Lead 1 is evidence of widespread changes in the retreat of activation of the heart. In part this is attributable to the increase in muscle mass with a consequent tendency for the pattern of invasion to determine the pattern of retreat. In addition, however, widespread changes in the conduction system which develop in hypertrophied hearts may be an important contributing factor. This damage to the conduction system may be insufficient to prolong QRS while giving the electrocardiogram the other characteristics of intraventricular block. That this latter factor may play a rôle is shown by the gradual evolution of the left ventricular strain curves in a number of cases into the common type of intraventricular block. The damage to the con-

duction system may result from chronic coronary insufficiency, consequent upon coronary sclerosis and arterial narrowing to which the conduction system is more susceptible than ordinary heart muscle.[23] Coronary sclerosis is not the only factor involved in these conduction disturbances as these changes occur in relatively young patients who have chronic rheumatic valvular disease (Fig. 2, *C*). Wearn *et al.*[18] have shown that as the heart hypertrophies the capillary supply becomes insufficient and not commensurate with the increase in mass of the myocardium. This is probably an important factor in the production of conduction disturbances in hypertrophied hearts and could explain the 4 cases of Rykert and Hepburn[19] in which at autopsy myocardial hypertrophy was found without other abnormalities and with normal coronary arteries.

These *S–T–T* changes resulting from abnormalities in conduction must not be confused with those changes resulting from injury currents even though both are the result of coronary insufficiency. The *S–T* segment deviation expressing injury currents is not always deviated in a direction opposite to the major *QRS* deflection as is the case with a conduction disturbance. It has its convexity directed in the same direction as its deviation, unlike the case with a conduction disturbance where the convexity is in the opposite direction to the deviation of *S–T*. Furthermore, in injury currents the *T* wave is in the opposite direction to the *S–T* deviation, while in the full-blown conduction disturbance the *T* and *S–T* are deviated in the same direction. The close relation of the left ventricular strain curve to intraventricular block is shown by the development of the latter in long-standing cases. In such circumstances the appearance of the curve does not change usually except that *QRS* becomes prolonged beyond 0.12 second. It is true that occasionally injury currents may produce *S–T* segment or *T* wave changes in cases of left ventricular strain which are confusing, and sometimes the early stages of left ventricular strain give records which may be mistaken for those of injury currents. Usually, however, the *QRS* changes that occur and the typical *S–T–T* patterns of injury currents are sufficiently distinct from those resulting from the conduction disturbances seen in left ventricular strain (and in the common type of intraventricular block). In some instances, little help is to be expected from the chest leads in this differentiation, since the *QRST* findings may be similar regardless of whether the cause is injury currents or a conduction disturbance.

The importance of recognizing the *S–T–T* changes in Lead 1 of left ventricular strain lies in the evaluation it affords in determining the normality of axis deviation. We are designating any record that has merely an inversion of the major phase of QRS_3, with no associated *S–T–T* changes in Lead 1, or Leads 1 and 2, as a normal phenomenon provided the inverted phase is not of the *Q* type, and are labelling this, left axis shift. It has been adequately shown[5]

that about one-fourth of normal patients of middle age will show this simple left axis shift, and that this is especially true when obesity[16] or pregnancy[10] is present. The presence of an associated inversion of QRS_2, in addition to that of QRS_3 without the Q pattern, is to be regarded as probable evidence of left ventricular strain, and is called the first type with axis deviation. It has nevertheless been shown that such marked axis deviation may be found in

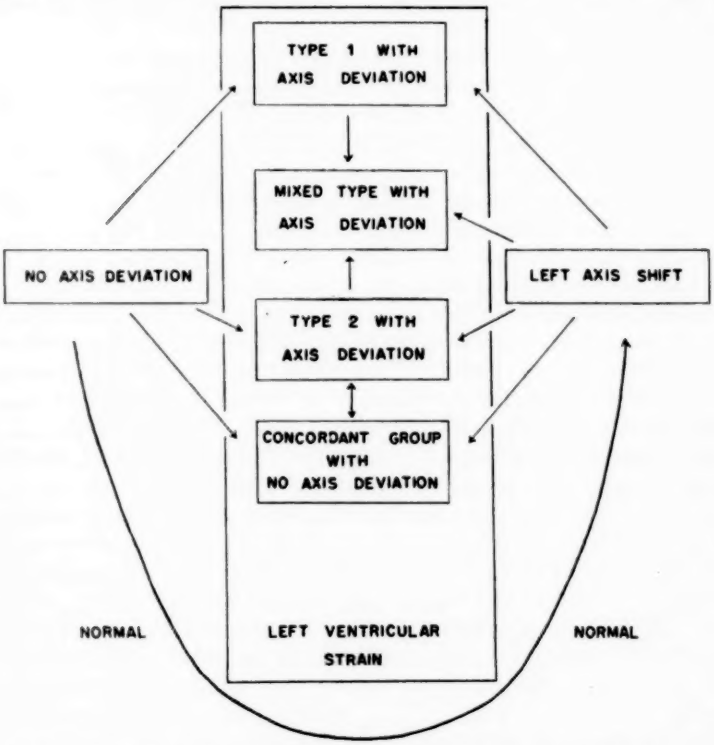

FIG. 8.—The interrelationship and the manner of their progression of the various types of electrocardiograms seen in left ventricular strain, found in the present series.

brown atrophy of the heart,[9] and therefore may not always be indicative of left ventricular hypertrophy. While the normal left axis shift or the first type with axis deviation may be found in cases of left ventricular hypertrophy, the presence of the S–T–T deviations described in this report are the distinguishing features of prolonged left ventricular strain, and are indicative to us of the presence of left ventricular preponderance. With these S–T–T changes, the presence of axis deviation is not a necessary accompaniment for the diagnosis of differential predominant ventricular strain and is in fact sometimes absent.

The practical importance of recognizing these changes in Lead 1 occurring in left ventricular strain is obvious. Especially one must be careful not to label the case an instance of recent myocardial infarction with its clinical implications. The classical forms may be present in patients who are ambulatory and have a circulatory system consistent with a moderately active existence. The concordant group is as important and as diagnostic as the classical type of left ventricular preponderance electrocardiograms and as such must be recognized.

The relationship in the development of the various types of electrocardiographic pattern in left ventricular strain according to our experience is summarized diagrammatically in Figure 8.

Summary. 1. The electrocardiographic patterns seen in 178 instances (24 necropsied) of left ventricular strain are described.

2. The characteristic development of the classical S–T–T complex in left ventricular strain is emphasized.

3. The classical types and intermediate forms are described and the natural evolution of these are presented.

4. Approximately 15% of the total cases in the present series did not show any axis deviation and 62.5% of these had the classical S–T–T deviation in Lead 1. This latter type is called the concordant type of left ventricular strain. It formed 19% of all the cases with characteristic S–T–T changes in Lead 1.

5. It was not possible to correlate heart size and the type of electrocardiographic pattern in left ventricular strain.

6. Accompanying right ventricular strain, either as a late result of left ventricular strain or of an associated independent cause, and changes in the heart's position are the probable chief causes for lack of axis deviation in the concordant type of left ventricular strain.

7. The S–T–T deviation in left ventricular strain is attributable to a disturbance in the retreat of activity in the ventricles, in part due to the hypertrophy itself and in part secondary to coronary insufficiency.

8. The practical importance of recognizing the concordant type of electrocardiogram in left ventricular strain is emphasized.

We are indebted to the several physicians of the hospital staff for permission to use their cases, to Dr. R. Arens of the *X*-ray Department for use of the teleoroentgenograms and to Dr. O. Saphir of the Pathology Department for use of the necropsy reports. We wish to acknowledge the assistance of Drs. J. Post and H. Sugarman in the compilation of the material.

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THE ALTERATIONS OF THE T-WAVES CAUSED BY A CHANGE OF POSTURE.

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In one of his early classical papers on the normal electrocardiogram Einthoven[4] described the alterations which occur with change of position of the patient. Since then the subject has been investigated frequently, but for many years attention was directed exclusively to the alterations of the initial ventricular complex. There is a rather voluminous literature dealing with changes of this type noted after change of position and movement of the diaphragm.[3]

It has also been known for a long time that the *T*-wave may become altered and even inverted on change of posture; in fact, in 1910, Grau[7] described alterations of the *T*-waves in healthy subjects as the result of gastric distention. He also found changes in the *T*-waves with change of posture. More recently Leimdoerfer described alterations of the *T*-waves in Leads I and II upon change from the recumbent to standing posture. He found inversion of the *T*-waves and depression of the *S–T* segments, especially in Leads I and II, after prolonged standing in patients with myocardial damage, but never in healthy individuals. He recommended that the electrocardiogram be taken after standing for 10 to 15 minutes as a functional cardiac test. At the same time, however, Åkesson found alterations of the *T*-waves when the normal subject maintained the erect posture, and explained them as the result of an orthostatic anemia of the heart; this is caused by a redistribution of blood in the standing individual. In the past few years several studies have been undertaken with regard to these changes. Some investigators have interpreted the alterations of the *T*-waves as a

normal phenomenon,[5,20] while others have regarded them as a sign of myocardial damage,[1c,18,19] or evidence of a pathologic heart.[9,13]

The appearance of these changes in the normal may be regarded as a demonstrated fact. However, there is no unanimity of opinion with regard to the mechanism involved. A reinvestigation of this question was undertaken and an endeavor was made to find a satisfactory explanation for it. In this study the alterations of the final deflection have received primary consideration and discussion.

Results. All our investigations were conducted on normal adults without any evidence of heart disease; the age of the patients ranged between 20 and 30. Thirty-five patients had electrocardiograms taken in the supine position and then were requested to stand for a period not exceeding 12 minutes. Electrocardiograms were taken at short intervals when the patients were in the upright position. The results were fairly uniform whether the electrocardiograms were taken immediately or after 12 minutes of standing. Table 1 shows the results with regard to alterations of the form of the *T*-waves, as compared with the *T*-waves obtained when patients were recumbent.

TABLE 1.—ALTERATIONS OF *T*-WAVES.

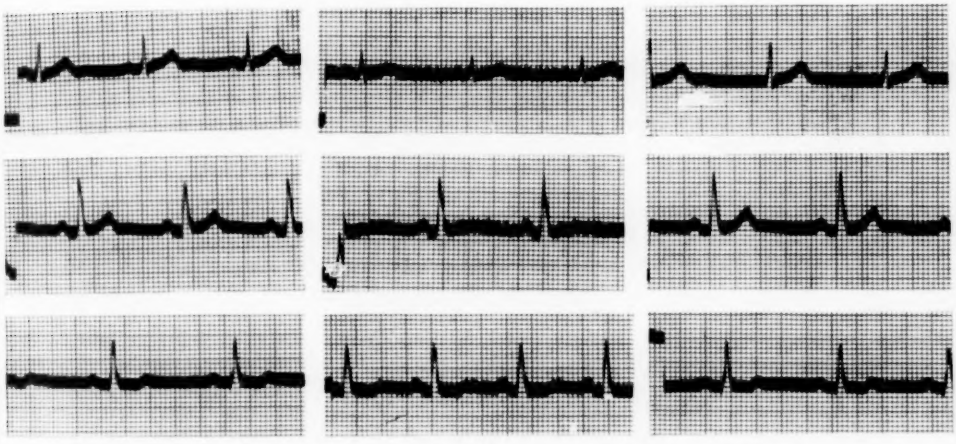
	Lead	No. of cases	No. showing diminution	No. showing increase.	No. showing no change.
Alterations of *T*-waves on change of position from horizontal to vertical	I	34	22	4	8
	II	35	31	0	4
	III	34	31	0	3
Alterations of *T*-waves on deep inspiration	I	15	15	0	0
	II	15	14	1	0
	III	15	8	4	3
Alterations of *T*-waves on deep expiration with abdominal pressure	I	15	0	15	0
	II	15	0	13	2
	III	15	12	2	1

The changes were characterized by a depression of the height of the *T*-waves in all leads. The change in Lead I, however, was very slight, whereas in Lead II, and especially in Lead III, it consisted of a marked flattening or inversion of the *T*-wave. In only 3 cases did the *T*-wave remain unchanged in Lead III when the patient stood. In 9 cases a *T*-wave in Lead III, previously positive, became inverted. Depression of the *S–T* segment in Lead III occurred 8 times.

In 28 instances the electrocardiogram was again taken immediately after the patient reassumed the supine position. In all cases the *T*-waves *immediately* returned to their former height and configuration.

In 7 of 35 cases a diminution in the height of the *P*-waves in Lead I occurred while the patient was standing, and in 21 cases an increase in the height of the *P*-waves was observed in Lead III. The alterations of the *QRS* complexes were slight. In 9 cases there was a tendency toward right axis deviation on standing, but this returned to normal immediately on lying down.

Figure 1 shows the electrocardiogram of a 25-year-old male in good health in the supine position (Fig. 1*a*). The *T*-waves are positive in all leads. The second series (Fig. 1*b*) was taken while the patient was standing. It shows a lower *T*-wave in Lead I, an almost invisible *T*-wave in Lead II, and an inverted *T*-wave in Lead III. Immediately after lying down the electrocardiogram (Fig. 1*c*) is again like the first one, taken while the patient was in the supine position.



a *b* *c*

FIG. 1*a–c*.—*a*, Patient in the supine position; *b*, immediately after standing up; *c*, immediately on lying down.

These results are in full agreement with those of previous workers. Åkesson[1a] found an inversion of T_3 in 31% of his cases while standing. According to Erkelens the *T*-waves in Lead III became inverted in 15 out of 61 cases while standing, a total of 24.5%.

It has already been proven that the alterations described are not evidence of myocardial damage, since they are just as common in the healthy as in patients with heart disease.[5,20] In order to rule out the possibility of coronary insufficiency[18,19] or orthostatic anemia of the heart,[1b,c] we decided first to examine the electrocardiogram in the standing patient after physical effort in the hope that an eventual disturbance of the cardiac blood supply would be more clearly visible after effort; second, to examine the electrocardiogram after the administration of $\frac{1}{100}$ gr. of nitroglycerine, in the hope of abolishing changes due to a diminished blood supply to the heart.

The exercise consisted in hopping 50 times, first on one foot and then on the other. The electrocardiogram was taken after the exercise in 26 cases with patients in the standing position. In all cases only the usual physiologic changes occurred. The *T*-wave became higher in all leads, the *S–T* segment became slightly de-

pressed, and a formerly inverted *T*-wave (while standing) in Lead III became less inverted, invisible, or even positive. There was never an increased negativity of the *T*-waves or a pathologic depression of the *S–T* segment, immediately or 1 to 5 minutes after the exercise.

The electrocardiogram was also taken after the administration of nitroglycerine ($\frac{1}{100}$ gr.) while the patient was still standing. The electrocardiogram, registered at intervals up to 5 minutes after nitroglycerine was given, showed a tachycardia in 6 out of 30 cases tested, further depression of the *S–T* segment, especially in Leads II and III, and a still further diminution of the height of the *T*-waves.

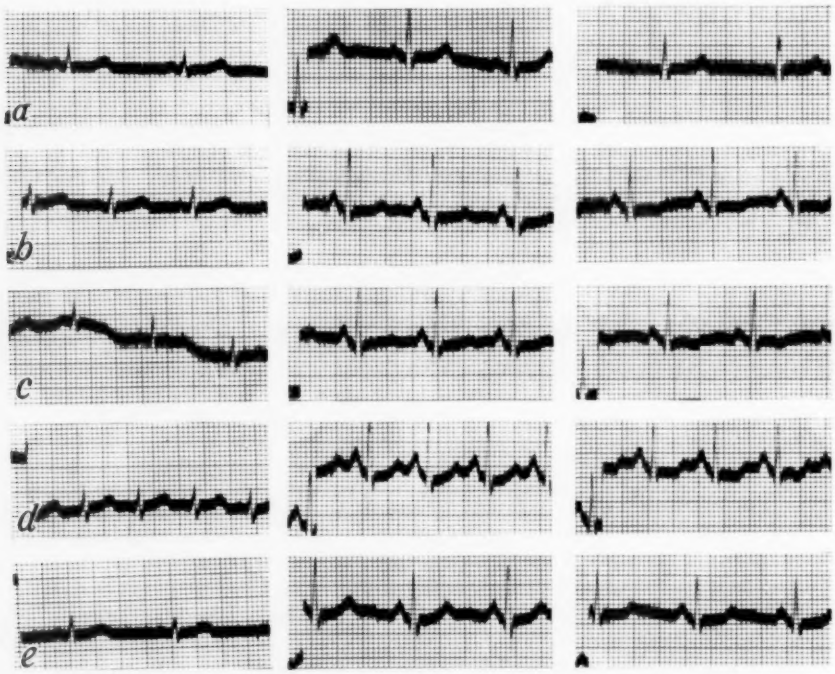


FIG. 2*a–e*.—*a*, Patient in the supine position; *b*, standing; *c*, after exercise while still standing; *d*, after nitroglycerine while standing; *e*, immediately on lying down.

In the first series of Figure 2 there is a normal electrocardiogram taken from a 26-year-old healthy young man. The *T*-waves are positive in all leads. The second series (Fig. 2*b*), taken after the patient stood 5 minutes, shows larger *P*-waves in Leads II and III, and smaller *P*-waves in Lead I. The *T*-waves are lower in Lead II and definitely inverted in Lead III. No marked changes appeared after exercise (Fig. 2*c*). Two minutes after the administration of $\frac{1}{100}$ gr. of nitroglycerine the rate increased from 90 to 110 per minute (Fig. 2*d*), the *S–T* segment became markedly depressed in Leads II and III, and the *T*-wave in Lead III became more inverted than

before. The fifth series (Fig. 2*c*) was taken immediately on lying down. The heart rate diminished to 80 per minute, the *T*-waves became normal, the *S–T* segments in Leads II and III are still slightly depressed as a result of the nitroglycerine. The inversion of the *T*-wave in Lead III which appeared in the erect position never disappeared after the administration of nitroglycerine.

From these results one may conclude that anoxia of the heart, as well as an insufficient blood supply, do not play any rôle in the formation of the described alterations of the *T*-waves. Since a change of position of the heart within the chest seemed the next most probable explanation of the alterations of the *T*-waves, we took electrocardiograms while the patient was recumbent, while standing, and then, while the patient was still standing, in full inspiration and expiration.

FIG. 3.—Lead II. First tracing, patient in the supine position; second, in erect position; third, during deep inspiration; fourth, during deep expiration, while still standing.

Figure 3 shows 4 electrocardiograms, each taken in Lead II. The first shows the normal tracing taken while the patient was supine; the second while he was standing. The formerly normal positive *T*-wave became inverted. The third tracing was also taken while the patient was standing, but during maximum inspiration. It shows increased inversion of the *T*-wave. Without a change of posture the patient was asked to exhale completely. The *T*-wave became immediately positive (fourth tracing).

Figure 4*a* shows a right axis deviation registered in a healthy

individual. The *T*-waves were positive in Leads I and II, and negative in Lead III. This negativity increased in Lead III when the electrocardiogram was taken while the patient stood (second

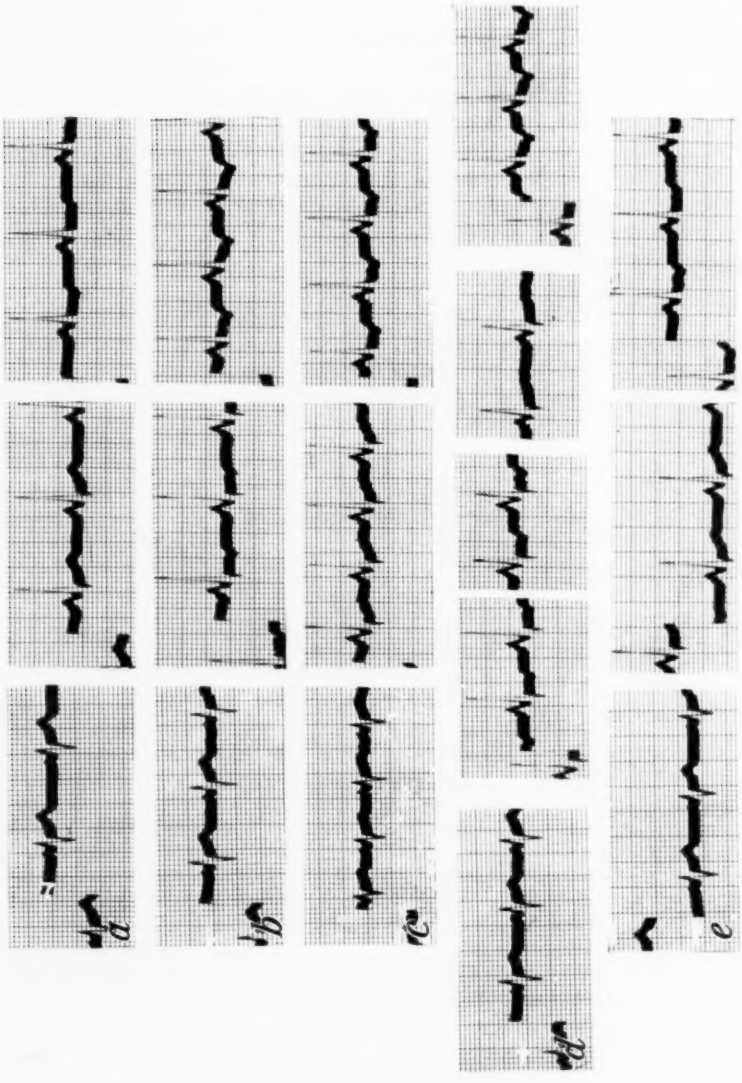


FIG. 4*a-d.*—*a*, Three limb leads with the patient lying flat; *b*, while standing; *c*, after exercise; *d*, after nitroglycerine, while still in the upright position. The second lead was taken in three sections; first, while the patient was breathing normally; second, during deep inspiration; third, during deep expiration; *e*, immediately after lying down.

series). The *T*-wave in Lead II also became negative. After exercise the *S–T* segment became slightly depressed (Fig. 4*c*), and the *T*-wave less negative. The administration of $\frac{1}{100}$ gr. of nitroglycerine increased the depression of the *S–T* segment and the negativity of the *T*-waves in Leads II and III (Fig. 4*d*). The electrocardiogram in Lead II was also taken in deep inspiration. It shows a marked increase in the negativity of the *T*-wave (third tracing in the fourth series). Then the electrocardiogram was taken in deep expiration with upward pressure of the diaphragm by means of a large rubber balloon (fourth tracing in the fourth series). The *T*-wave became isoelectric. Immediately after the patient lies down, the electrocardiogram (Fig. 4*d*) is almost normal. The slight tachycardia and depression of the *S–T* segment in Lead II are still the consequence of the nitroglycerine.

The electrocardiogram was examined in deep inspiration and expiration 15 times. In all but one case the *T*-wave became more inverted in inspiration, and much less inverted or normal in expiration combined with abdominal pressure as seen in Figures 3 and 4. In only one case (Fig. 5) were the changes exactly opposite; namely, higher *T*-waves in Lead III in inspiration, and inverted *T*-waves in expiration. In this case, however, there were also very marked changes in the initial complex. In the supine position this patient showed normal positive *T*-waves in Leads I and II; the *T*-wave in Lead III was low and preceded by a slightly depressed *S–T* segment (first series). In the upright position, the *S–T* segment in Lead III became more depressed (second series); during full inspiration (third series) the initial complex in Lead I became smaller and the *T*-wave in Lead III became positive. During expiration and abdominal pressure (fourth series) left axis deviation appeared, and the *T*-wave in Lead III became inverted. Immediately on the patient lying down, the electrocardiogram returned to normal.

Changes in the form of the *T*-waves in Lead III during deep respiration have been known to occur in the healthy. Scherf and Boyd[17] described a case with a right axis deviation and a negative *T*-wave in Lead III in inspiration, and a left axis deviation and a positive *T*-wave in Lead III in expiration. Such marked changes are rare when the patient is recumbent. The quick and frequent change in the form of the *T*-waves in the third lead during respiration in the patient while standing is remarkable. From these tracings we may conclude that a rapid change in the position of the heart, as occurs during deep inspiration and expiration, may markedly influence the form of the *T*-waves in Lead III (and II).

Discussion. It has been pointed out that the inversion of the *T*-waves in Leads II and III in the standing patient cannot be regarded as a sign of a myocardial lesion. It is necessary to determine whether these changes are due to coronary insufficiency or anoxia of the heart (orthostatic anemia), or whether they are due to

mechanical, physical factors. At the outset there are a few arguments which speak against the assumption of an anoxia of the heart or parts of it. First, the form of the alterations of the final deflection deserve consideration. In the erect posture one usually finds only an inversion of the *T*-wave in Leads II and III, but rarely a marked depression of the *S–T* segment. Pronounced depression of the *S–T* segment, however, is characteristic of coronary insufficiency and a reduced blood supply to the heart. Changes of the *T*-waves alone are found only in very circumscribed cardiac damage such as in coronary occlusion, myocarditis, and so on. In the exercise test,[6] or the anoxemia test[12,15] the *S–T* segment is primarily altered.

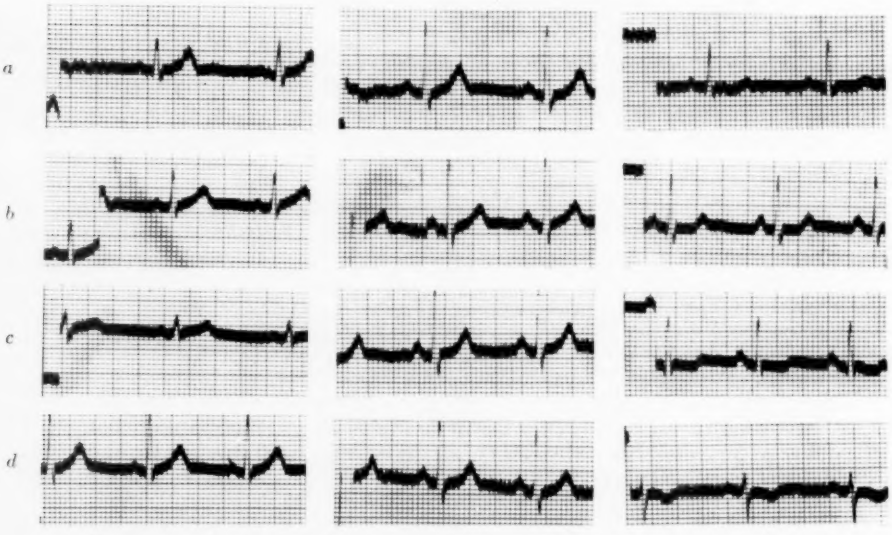


FIG. 5*a–d*.—*a*, Patient supine; *b*, erect position; *c*, during deep inspiration; *d*, during deep expiration, while standing.

Second, the alterations of the electrocardiogram in anoxia disappear slowly. It may even require as long as 30 minutes before the electrocardiogram will assume its usual form. The changes in the *T*-wave caused by a change of posture disappear immediately upon lying down. Third, a few minutes after the anoxia of the heart caused by physical effort in coronary stenosis subsides, frequently the *T*-waves are unusually high for a short time. This has been explained[6] by a reactive hyperemia following diminished cardiac blood supply and anoxia. We never encountered these changes after the patient had been standing. Fourth, upon the assumption of an upright position the electrocardiogram never revealed an inversion of the *T*-wave in Lead I, which is a common event in general anoxia.

The result of the investigations reported in this paper show that change of position of the diaphragm in different phases of respiration in the standing patient causes marked alterations of the electrocardiogram to appear, and that the inversion of the *T*-wave, which develops when the patient stands, disappears in complete expiration; this speaks definitely against the assumption of any coronary insufficiency, myocardial damage, and so on. Furthermore, if anoxia were the cause of the changes described, then exercise should increase them and nitroglycerine should abolish them. However, just the opposite occurred. As is typical for the healthy heart and the heart without impairment of blood supply, the *T*-waves became higher on exercise, and lower following nitroglycerine. The latter effect may be due to the tachycardia and fall of blood pressure, both of which cause a diminished cardiac blood supply. It is also possible that the dilatation of large areas in the splanchnic field still further diminishes the myocardial blood supply. Furthermore, prolonged standing does not accentuate the changes. The results were the same whether the electrocardiogram was taken immediately on standing or after 12 minutes in this position. We could not confirm the findings of others[18] who reported that the electrocardiogram taken immediately after standing showed less alteration than that taken a few minutes later, a fact which has been used as an argument in favor of an orthostatic anemia. The findings also bore no relationship to the blood pressure. The blood pressure might rise or fall slightly on standing, but the alterations were the same.

A diminished blood supply may play a rôle in cases of marked postural hypotension, as described by Sanders,[16] but in our cases the blood pressure remained unchanged or did not change markedly during the alteration of posture. Obviously the findings must be physiologic and depend on posture and the position of the heart in the thoracic cage. The importance of the relationship between the heart and the diaphragm and other neighboring tissues in regard to the form of the *T*-wave has been pointed out.[10,11,14,20] The assertion of different authors that the electrical axis of the main deflection frequently shifts to the right on standing while the axis of the *T*-waves shifts to the left (therefore a change of position cannot play a rôle),[5,19] would be valid only for direct leads or under conditions of constant equal conduction of the electrical forces from the heart by adjacent tissues. This condition did not prevail in our investigations.

Since the electrocardiogram is frequently taken in the sitting position, even at present in some institutions, and since the *T*-waves in Leads II and III may become inverted under such circumstances,[1b] it is evident that at times serious errors may be made. We have frequently seen the diagnosis of posterior wall infarction made on the basis of an inverted *T*-wave in Leads II and III in the healthy individual. The report of "abnormal T-waves" in the healthy

young person, occasionally encountered in the literature,[2-8] may be due to the fact that the electrocardiogram was obtained while the patient was sitting. These papers do not mention in which posture the electrocardiograms were taken, but in all such reports the *T*-waves were like those of patients who have been standing, namely, inversion in Lead III, less in Lead II, and never in Lead I.

Body build is an important factor in the production of the changes described above, since asthenic individuals more frequently show the inversion of the *T*-wave in Lead III.[5]

Since the appearance of inverted *T*-waves in Leads II and III when the examination is made with the patient erect is explained by a change of the position of the heart in relation to the neighboring tissues, particularly the diaphragm, it might be anticipated that the same changes would occasionally appear in a normal person while supine; this would occur if the heart happens to have a position similar to that of other persons when the latter are standing.

FIG. 6.—A 27-year-old healthy female while lying down; the upper tracing during normal respiration; lower, at the end of a deep expiration with her belt on.

Figure 6*a* was obtained from a 27-year-old woman who complained of palpitation, independent of effort. Physical examination revealed a short female, rather stocky in build with an unexpectedly small heart which was placed symmetrically in the midline and which barely touched the diaphragm. There was no evidence of an organic cardiac lesion. The electrocardiogram, recorded with the patient in the supine position, revealed low voltage in Lead I; the *T*-wave in Lead II was almost invisible and in Lead III it was inverted. These changes were identical with those noted in tracings of normal patients in the upright position.

The patient was asked to put on an abdominal belt for a moment; Figure 6*b* was taken during maximum expiration while the patient remained in the supine position. The *T*-waves became normally positive in Lead II and less inverted in Lead III.

Conclusions. The phenomenon of flattening or inversion of a formerly positive *T*-wave in Lead III in the upright position was studied in 35 patients. This inversion increased during deep inspiration and decreased at the end of maximum expiration with upward pressure on the diaphragm.

These observations speak against the assumption that cardiac damage or anoxia of the heart muscle can be the factor responsible

for the electrocardiographic alterations. They confirm the conception that the inversion of the *T*-wave is due to a change in posture, and therefore a change in contact between the heart and the neighboring tissues.

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FAT TOLERANCE TESTS IN PSORIASIS.

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In recent years there has been a growing impression that there is an underlying disturbance in fat metabolism in psoriasis. In 1933, Grutz and Burger[14] expressed the view that psoriasis is probably based on either of two possible explanations: 1. There may be a greater accumulation of fat in the blood than the skin is physiologically able to handle; this fat, being excreted from the blood through the skin capillaries, streams into the epidermis and produces the phenomenon of psoriasis. 2. Fats may be formed in unphysiologic structure or in incorrect proportions of their component fractions. These authors favored the first theory and most of the subsequent investigations are based on their work.

In an excellent review of theoretical, clinical, biochemical and therapeutic considerations in psoriasis, Gate, Chanial, Vallet and Humbert[10] noted:

1. The greater frequency of psoriatic lesions in otherwise healthy and well-nourished subjects; in individuals whose diets are especially

rich in proteins and fats; in winter when fats are taken in larger amounts. They mentioned the frequently noted decrease of psoriasis in Germany during the war years 1914–1918 which coincided with a very great curtailment in fat consumption. (It is apparent that the restriction was due to the shortage of butter, milk, cream, bacon and meats.)

2. The abnormally high content of lipoids in psoriasis scales.

3. The commonly reported disturbance in fat metabolism in psoriasis as shown by:

(*a*) Retention of lipoids in the blood.

(*b*) General elevation of the degree of lipemia.

(*c*) Frequent hypercholesteremia which some researchers consider as evidence of lipoid retention in general.

(*d*) Alimentary hyperlipemia.

4. The amelioration in psoriatic lesions, without local therapy, by methods intended to reduce hyperlipemia and hypercholesteremia, the best results being shown by a very low fat diet.

Most studies in alimentary hyperlipemia are based on the early observations of Flint[7] in 1862, following which many investigators using various methods adequately demonstrated the rise in blood fats after fat feeding. As employed by Grutz and Burger,[14] and practically all workers who studied their observations, the technique consisted in feeding 5 gm. of cholesterol in 100 gm. of olive oil and examining the cholesterol content of the blood at 4, 8, and 12 hour intervals. While it is true that no procedure based on the feeding of a large quantity of a single food substance can give an accurate picture of the organism's ability to handle that substance, in our opinion the method of Grutz and Burger represents a wider departure from average diet and normal physiology than is necessary. Since it is well known that the feeding of neutral fats will produce a rise in blood cholesterol,[3,15,30] ingestion of cholesterol as part of the test fat meal is unnecessary. Furthermore, cholesterol is characteristic of animal fats,[2] being absent in vegetable fats; it is therefore more likely that a great increase in blood cholesterol will follow the feeding of animal fat. It is also noteworthy that in the average diet the bulk of the fats are of animal origin. While there is definite evidence to the contrary,[30] it has been stated that the changes in the total cholesterol of the blood after a fat meal are slight and inconstant.[4a] This has led most students of the problem of fat metabolism in psoriasis to study only plasma cholesterol and cholesterol esters, disregarding the function of the free cholesterol contained in the red blood cells. Yet Knudson[18] concluded that the red blood corpuscles play a very active part in fat metabolism.

It has been stated that a minimum of 3.5 gm. of fat per kilo of body weight is needed to produce consistently alimentary hyperlipemia.[22] Boyd[6] objected to this amount on the ground that it indicated an unphysiologic intake of 200 gm. of fat per meal.

We have accordingly used a procedure which more closely approximates the average diet. Other observers[1,5a,b,8,11,26,31] have shown that this method, or some modification of it, definitely yields a frank rise in blood cholesterol. We have been able to produce alimentary hyperlipemia consistently by using in a test meal (to be described below) 100 gm. of fat. Such an amount is roughly comparable to the 1.75 gm. of glucose per kilo of body weight commonly used in sugar tolerance tests.

Most of the observers who studied fat metabolism in psoriasis collected blood samples at 4, 8, and 12 hour intervals after the fat meal. As Wechsler[33] has stated, "Even a cursory review of the literature indicates that a typical curve has not been obtained." We feel that in order to note even slight variations in blood constituents after a test meal an interval of much less than 4 hours is imperative. In our determinations the total cholesterol of whole blood was used as a measure of hyperlipemia.

Procedure. After a 12-hour fast a blood specimen was taken. The patient was then given 500 cc. of 20% cream, representing 100 gm. of fat. Blood specimens were obtained at intervals of 1½, 3, 4½, 6, and 7½ hours and the whole blood was examined for total cholesterol by the method of Bloor.[45] During the time of the test the patient was allowed to take very occasional sips of water. Most of the patients were ambulant but activity was closely restricted.

Material Studied. In this investigation 10 patients with unequivocal psoriasis were studied (see Table 1). Of these, 6 were males and 4 were females. Their ages ranged from 22 to 75 years. The duration of their psoriasis varied from 2 to 40 years. The severity of the lesions varied from a few small discoid areas on the extremities to large, generalized areas distributed over the trunk and extremities. Two of the female patients (Cases 2 and 3) had each had 2 pregnancies. An arbitrary figure of 10% above or below average "normal" weight for age, sex, and height was used to determine whether the patient was obese or underweight. By these very narrow standards Case 2 was 24% and Case 8 was 10% overweight; Case 5 was 15% and Case 7 was 14% underweight. Excluding the obesity or underweight as already noted, none of these 10 patients had any complaints or abnormalities other than psoriasis, except Case 3 who had a small fibromyoma of the uterus.

As controls, 13 patients without evidence of past or present chronic skin disease were studied. Of these patients, 5 were males and 8 were females. Their ages ranged from 20 to 65 years. Seven patients were free of any apparent metabolic disturbance. Three patients (Cases 8, 9, 10) had well-controlled diabetes mellitus and 1 of these (Case 8) had in addition mild nephritis of the nephrotic type. There was 1 case of hyperthyroidism (toxic adenoma—Case 5), 1 of hypoparathyroidism (Case 11), and 1 of hypothyroidism (Case 13). The cases of diabetes mellitus and the thyroid

dyscrasias were especially included because of their well-known tendency to altered fat metabolism. By the same criteria as used for the psoriatic cases, Case 8 was 10% and Case 12 was 26% overweight; Case 1 was 12%, Case 5 was 24% and Case 7 was 16% underweight.

TABLE 1.—DATA ON CASES OF PSORIASIS AND NON-PSORIASIS.

Psoriasis.

Case No.	Age.	Sex.	Nude wt.	Normal wt.	Over-wt., %.	Under-wt., %.	Distribution of lesions.	Activity of lesions.	Duration in years.
1	75	M	145	135	7	..	Elbows, knees, back, groin	3+	40
2	47	F	173	139	24	..	Right knee and elbow	2+	27
3	34	F	128	124	3	..	Elbows, knees, left foot	3+	15
4	35	F	116	126	..	8	Elbows, knees, back, abdomen	4+	20
5	27	M	138	163	..	15	Elbows, knees	2+	2
6	22	F	108	116	..	7	Elbows, knees	2+	3
7	58	M	146	170	..	14	Elbows, knees, back, chest	4+	25
8	25	M	163	147	10	..	Elbows, chest, back	1+	4
9	22	M	139	136	2	..	Elbows, trunk	4+	4
10	55	M	143	150	..	4	Generalized	4+	30

Non-psoriasis.

Case No.	Age.	Sex.	Nude wt.	Normal wt.	Over-wt., %.	Under-wt., %.	Diagnosis.
1	26	M	149	171	..	12	Chief complaint: thinness; totally negative history and physical
2	35	F	132	127	4	..	Lumbosacral strain
3	20	F	113	121	..	6	Nephroptosis, irritable colon
4	32	F	117	122	..	4	Irritable colon
5	39	F	105	139	..	24	Hyperthyroidism
6	63	M	146	150	..	2	Duodenal ulcer
7	31	M	120	143	..	16	Healed pulmonary tuberculosis
8	48	F	148	134	10	..	Controlled diabetes mellitus, mild nephrotic type nephritis
9	52	F	150	139	7	..	Controlled diabetes mellitus
10	65	M	141	155	..	9	Controlled diabetes mellitus
11	54	F	142	143	..	..	Hypoparathyroidism
12	44	F	176	139	26	..	Hypertension
13	24	M	176	153	15	..	Hypothyroidism

Results. (See Table 2.) The fasting total cholesterol levels in 10 cases of psoriasis lay between 150 mg. and 312 mg. per 100 cc. of whole blood, the average being 192 mg. (Fig. 1). Only 1 patient revealed a fasting blood cholesterol above the highest commonly accepted normal level of 240 mg. per 100 cc. of blood (Case 10). This patient, however, had the most severe and most widely distributed psoriatic lesions. The degree of rise from fasting to the highest level of blood cholesterol varied from 31.9% to 108%, the average being 51.4% (Fig. 2). The highest level of blood cholesterol was attained in 1½ hours in 1 case or 10% of the cases, 3 hours

in 2 cases (20%), 4½ hours in 4 cases (40%), 6 hours in 2 cases (20%), and 7½ hours in 1 case or 10% of the psoriasis cases studied (Fig. 3).

In the 13 control patients the fasting total cholesterol ranged from 123 to 250 mg. per 100 cc. of whole blood, the average being 188 mg. (Fig. 1). The degree of rise from fasting to peak level ranged from 25% to 112%, the average rise being 62.8% (Fig. 2). The highest level of absorptive specimen was obtained in 3 hours in 2 cases (15.4%), 4½ hours in 9 cases (69.2%), and 6 hours in 2 cases (15.4%) (Fig. 3).

TABLE 2.—BLOOD CHOLESTEROL.

Case No.	Fasting.	1½ hrs.	3 hrs.	4½ hrs.	6 hrs.	7½ hrs.	Time of peak.	Change, %.
Psoriasis.								
1	150	192	250	312	208	160	4½	108
2	151	160	192	...	208	160	6	37.7
3	160	208	217	227	192	184	4½	41.8
4	166	192	208	250	192	172	4½	50
5	166	178	200	217	227	217	6	36
6	166	185	...	208	178	150	4½	25
7	172	185	227	218	192	160	3	31.9
8	227	262	276	312	357	384	7½	68
9	250	454	312	250	208	192	1½	81
10	312	418	500	454	384	312	3	35
Non-psoriasis.								
1	123	132	147	151	166	151	6	35
2	138	156	171	227	171	147	4½	64
3	147	166	192	227	178	151	4½	54
4	147	192	227	312	250	...	4½	112
5	166	192	208	192	166	147	4½	25
6	166	192	250	276	250	192	4½	66
7	189	227	250	263	238	208	4½	39
8	218	276	416	357	340	270	3	90
9	227	238	250	333	277	172	4½	47
10	250	317	416	272	250	147	3	66
11	250	268	272	416	333	238	4½	66
12	250	312	357	416	312	227	4½	67
13	171	...	208	250	312	288	6	82

Total blood cholesterol in mg. per 100 cc. of whole blood.
Time of peak (highest blood cholesterol) in hours after ingestion of test meal.
Per cent of change from fasting blood cholesterol to level at peak of curve.

It is striking that this study indicates that in psoriatic patients there is no significant departure from non-psoriatics in the ability to metabolize fats, as judged by the rate of absorption from the intestine and the rate of disappearance from the blood stream, the total cholesterol of whole blood being used as a criterion. In fact, the group of patients without dermatologic lesions showed slightly higher fasting levels and a somewhat greater degree of rise above the fasting levels than the group of psoriatic patients.

In both groups, particularly in the non-dermatologic patients, there appeared to be a tendency for the thinner patients to exhibit smaller degrees of rise of the fat tolerance curves, while the obese persons tended to show higher peaks (Table 3). This phenomenon was previously demonstrated by Blotner.[5a,b]

Comment. It is common experience to find an elevation in the cholesterol and total fat of the blood in such conditions as nephrosis, hypothyroidism, diabetes mellitus, xanthomatosis or xanthelasma, and pregnancy. In xanthomatosis the cholesterol accumulates in

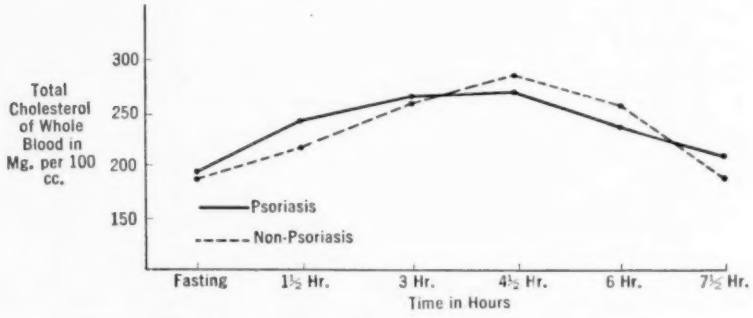

FIG. 1. COMPOSITE FAT TOLERANCE CURVES.

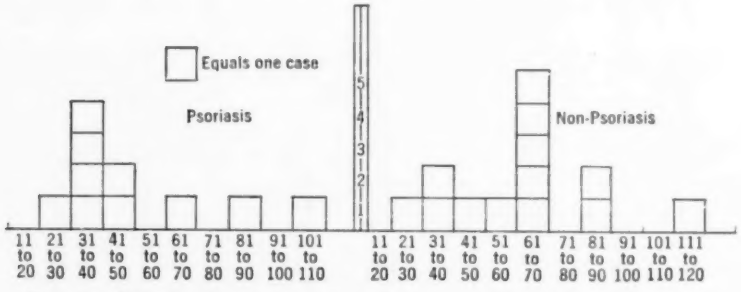

FIG. 2.—PERCENTAGE CHANGE FROM FASTING TO PEAK LEVEL OF BLOOD CHOLESTEROL.

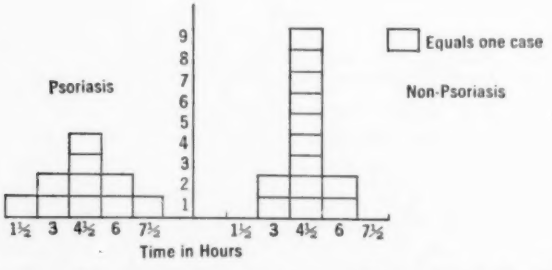

FIG. 3.—TIME OF HIGHEST BLOOD CHOLESTEROL LEVEL AFTER FAT TEST MEAL.

localized areas without disturbance of the epidermis or the most superficial layers of the skin. It is evident that the mere presence of hyperlipemia is not responsible for the production of lesions even remotely resembling those of psoriasis in this condition. In hypothyroidism even of advanced degree, where the skin is dry and scaly

and myxedema is marked, psoriasis is not a commonly observed feature. It has not been possible to find any reference in the literature to the regular coincidence of nephrosis and psoriasis.

Grutz and Burger[14] point to the "simultaneous or alternate occurrence of psoriasis and diabetes." Although our series is small, it is noteworthy that in a recent experience covering 64 patients with diabetes mellitus on the service of Dr. Mitchell Bernstein at Jewish Hospital we have not noted the coincidence of this disease and psoriasis. In a review of 500 cases of diabetes mellitus Greenwood[12] found 12 cases of psoriasis (2.4%), an incidence too small to suggest close association between these two diseases. According to Sutton,[29] psoriasis constitutes between 2% and 3% of average clinical experience, showing that diabetes mellitus bears no special relationship to psoriasis since these figures parallel those of Greenwood.

TABLE 3.—COMPARISON OF DEGREE OF RISE OF BLOOD CHOLESTEROL LEVEL WITH DEGREE OF OBESITY OR THINNESS.

Psoriasis.				*Non-psoriasis.*			
Case No.	Overweight, %.	Underweight, %.	Change of cholesterol, %.	Case No.	Overweight, %.	Underweight, %.	Change of cholesterol, %
6	..	7	25	5	..	24	25
7	..	14	31.9	1	..	12	35
10	..	4	35	7	..	16	39
5	..	15	36	9	7	..	47
2	24	..	37.7	3	..	6	54
3	3	..	41.8	2	4	..	64
4	..	8	50	10	..	9	66
8	10	..	68	11	..	..	66
9	2	..	81	6	..	2	66
1	7	..	108	12	26	..	67
				13	15	.	82
				8	10	..	90
				4	..	4	112

Arranged according to increasing degree of rise of blood cholesterol.

There is a physiologic increase in the cholesterol of the blood in the latter months of pregnancy. Not only is psoriasis a rare complication of pregnancy, but 2 of our patients (Cases 2 and 3) reported that during their pregnancies the psoriatic lesions improved progressively, only to recur some months after delivery. Numerous similar reports in the literature[9,17,19–21,24,28] indicate that psoriatics in whom pregnancy supervenes usually show marked amelioration of the lesions, often to the point of complete clearing of the skin, with exacerbation either shortly after parturition or at the termination of lactation. Progressive local betterment in psoriatic pregnant women would seem to be the result of physiologic withdrawal of cholesterol from the tissues. The same reasoning can be applied to the effect of marked limitation of diet, whether for therapeutic purposes or as the result of qualitative and quantitative restriction of diet during war times. Starvation usually causes hyperlipemia affecting all the lipoid constituents of the blood.[25] The improvement noted in the psoriatic lesions of patients maintained on diets

low in fats is by no means necessarily the result of an alteration in fat metabolism in the body as a whole. It is more likely the effect of mobilizing from all tissues essential substances, such as cholesterol, which are not being supplied by the diet. Marchionini, Manz and Huss[23] have shown that even in normal persons the skin lipoids are definitely influenced by fat feeding within a short time after the ingestion of a fat test meal. These authors have also demonstrated that the local effect varies according to the skin area examined. Removal of a substance from a tissue or area which cannot metabolize it normally should ameliorate local evidences of such faulty metabolism.

It is well known that the adrenal cortex not only is very rich in cholesterol and other lipoids[7] but probably exerts a more profound and direct influence on these substances than any other gland or organ.[16,27,32] In this connection should be noted the marked hypertrophy of the adrenal cortex which occurs physiologically during pregnancy.[13] The striking improvement reported by Gruneberg[13] in cases of psoriasis treated with adrenal cortical extracts or hypophyseal corticotropic hormone is apparently not specific in its local influence on the psoriatic lesions but more probably the result of the fat mobilizing action of the adrenal cortex, causing withdrawal of the lipoids from all tissues, including the skin.

Summary. Because of a growing tendency to attribute psoriasis to a generalized disturbance in fat metabolism, the fat tolerance was studied in 10 patients with this disease. Changes in the total cholesterol of whole blood were used as an index of the degree of alteration of the blood lipid level. The psoriatic subjects showed no significant changes as compared with 13 non-psoriatic patients acting as controls.

The incidence of psoriasis in conditions exhibiting hypercholesteremia or hyperlipemia, such as hypothyroidism, diabetes mellitus, xanthelasma, nephrosis and pregnancy was reviewed. Only pregnancy has a relationship to psoriasis and that influence is distinctly beneficial.

The amelioration of psoriasis in starvation, low fat intake, pregnancy and in individuals receiving adrenal cortical extract or hypophyseal corticotropic hormone is, in our opinion, the result of the mobilization of fats and lipoids from all the tissues. This removes locally, from the skin, substances whose presence is irritating.

Conclusions. We believe that it is reasonable to conclude from our studies herein presented that psoriasis is a disease due to conditions existing locally in the skin. It is possible that a generalized disturbance in fat metabolism may contribute to such local conditions. However, we have not been able to demonstrate in fat tolerance tests with more closely spaced blood samples than have heretofore been employed that such a generalized disturbance exists.

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URINARY EXCRETION OF SULFAPYRIDINE IN THE RAT.

A Relationship of the Liver to Urolithiasis.

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Sulfapyridine, like sulfanilamide, is excreted in the free and acetylated form in the urinary tract of man (Baines and Wien,[2] Ratish, Bullowa, Ames, and Scudi,[13] Marshall, Bratton, and Litchfield[11]). Unlike acetylsulfanilamide, acetylsulfapyridine is highly insoluble and urolithiasis has been found to result from the deposition of this substance in the urinary tracts of certain patients and experimental animals (Antopol and Robinson,[1] Gross, Cooper, and Lewis,[5] Long and Wood[19]). Preliminary studies (Ratish, Bullowa, Ames, and Scudi,[13] Scudi, Ratish, and Bullowa[16]) have indicated the presence of unidentified soluble excretion products in human urine following the administration of sulfapyridine. Recently it was announced

(Scudi[14]) that a hydroxysulfapyridine* and its very water-soluble glucuronide were isolated from dog urine. Since the dog does not acetylate the drug, rats were used in the present study because this animal, like man, excretes the drug in both the free and acetylated forms.

Experimental. White rats, weighing 175 to 225 gm., were placed in small metabolism cages in groups of 3 and kept on a diet of purina pellets and water *ad libitum;* in addition, 3 cc. of water per 100 gm. of body weight were given daily by stomach tube. Urine was collected over 24-hour periods and the volume and glucuronic acid content (Maughan, Evelyn, and Browne[12]) were measured. This experiment was repeated for 2 days with each group to measure the average daily output of glucuronic acid for control purposes. The animals were then given 1 gm. of sulfapyridine in aqueous suspension per kilo. body weight, daily for 12 days. Daily samples of urine were analyzed for free and acetylsulfapyridine (Bratton and Marshall[3]) as well as for glucuronic acid. Certain clinical reports have indicated a higher incidence of uroliths in children than in adults (Tsao, McCracken, Chen, Kuo, and Dale[15]). For this reason, 5 groups (5 animals per group) of young rats were similarly studied. The drug was suspended in 10% acacia and administered by stomach tube to a third series of 8 groups of rats, other conditions being maintained as in Series 1 and 2. Since gum acacia is a source of glucuronic acid, 2 additional groups of animals were given equivalent amounts of gum acacia and the daily glucuronic acid output was measured, but no increase beyond the norm was noted during a 2-week period.

In the interests of space only the results obtained in the third series of experiments are recorded (Table 1). Essentially the same results were obtained in the two previous series. The data indicate that sulfapyridine augments the glucuronic acid output. When groups of these animals were no longer fed sulfapyridine, their glucuronic acid output fell to normal, and upon readministration of the drug, the glucuronic acid was again increased.

Since appreciable variations occurred in the findings, the food intake was controlled more rigorously in another group of animals as follows: Each of 24 animals (3 rats per group) was given 3 cc. of a mash (50 gm. of 100 mesh purina chow per 115 cc. of water) per 100 gm. body weight 3 times daily. Bodyweight, water consumption, and urine volumes were measured daily. These did not vary significantly. After a control period of 5 days, during which the daily glucuronic acid output was measured, sulfapyridine (1 gm. per kilo.) was administered daily for 7 days and the urine was analyzed for glucuronic acid (Maughan, Evelyn, and Browne[12]), free sulfapyridine, and acetylsulfapyridine (Bratton and Marshall[3]).

During the first few days of sulfapyridine administration, there is no constant ratio between the urinary free and acetylsulfapyridine, as shown in Chart 1. The daily acetylsulfapyridine output reaches a reasonably constant level 24 hours after the first dose of the drug.

* This product is of interest in connection with redox theories of the mode of action of the sulfanilamide series of drugs.

After the fourth day a fairly constant output of free sulfapyridine is attained. The ratio is then approximately 3.5 to 1 at the dose level studied. This ratio is almost twice as great as the solubility ratio (2 to 1) of free and acetylsulfapyridine. Assuming saturation of the urine, 40% of the "free" sulfapyridine may be present in a soluble form. Maximal output of free sulfapyridine occurs on the 4th day following initiation of sulfapyridine administration (Chart 1), whereas maximal output of glucuronic acid occurs on the 5th and 6th days (Chart 2). A similar parallelism is shown in Table 1.

TABLE 1.—GLUCURONIC ACID OUTPUT IN MG./100 GM. BODY WEIGHT.

Group:	1	2	3	4	5	6	7	8
Average wt. per group:	664	795	774	582	662	494	533	670
Day								
1 (normal)	8.7	8.6	8.2	11.3	9.3	6.7	8.6	8.4
2* (normal)	7.8	8.5	9.9	12.0	11.1	6.6	9.4	7.3
3	14.3	13.6	15.0	19.2	18.6	7.1	15.0	15.5
4	19.7	13.5	17.8	25.6	17.7	7.5	18.2	13.2
5	30.8	24.2	12.5	20.2	19.1	16.3	22.3	19.4
7	18.5	20.4	9.9	23.6	15.6	21.8	19.8	15.5
15	11.9	19.0	16.9	12.4	19.6	14.2	8.1	
				Free Sulfapyridine.				
3	18.1	12.1	13.2	24.6	19.4	5.9	10.6	11.6
4	22.6	13.9	16.3	23.6	21.5	4.7	15.4	12.4
5	26.0	24.9	14.8	28.4	25.5	12.5	24.4	19.0
7	25.4	26.0	21.5	31.3	23.0	21.3	25.3	15.5
15	24.7	37.6	29.5	32.5	40.2	35.3	31.2	
				Acetyl Sulfapyridine.				
3	13.6	10.6	13.6	16.3	16.6	5.3	8.3	9.6
4	18.1	13.2	16.3	18.4	16.6	5.3	8.6	9.4
5	13.7	10.8	6.8	13.7	12.5	9.3	25.1	12.5
7	16.2	14.9	6.5	19.4	14.4	19.5	16.1	7.0
15	4.1	7.0	7.3	6.7	6.0	7.0	3.3	

* After the normal values were obtained, the animals were given 1 gm. per kilo. per day of the drug throughout the test period.

The influence of sulfanilamide and sulfathiazole upon the glucuronic acid output was similarly studied. Sulfanilamide, fed for 10 days, did not cause an increase beyond the normal level in 6 rats. Thus, at this dose level (1 gm. per kilo. per day), sulfanilamide is not excreted to any appreciable extent as a glucuronide. This does not eliminate the possibility of ethereal sulphate formation (Shelswell and Williams[17]). Sulfathiazole, similarly fed to 6 rats over a 10-day period, was intermediate between sulfanilamide and sulfapyridine in its effect upon the glucuronic acid output. This may indicate that part of the "free" sulfathiazole is excreted both as an ethereal sulphate and as a glucuronide.

Since the conjugation of an aglucone is a function of the liver, the following experiments were performed in order to study the effect of liver injury. Four groups of rats were given 0.35 cc. of chloroform in 0.5 cc. of sesame oil subcutaneously daily for 3 days. Three days after the last dose of chloroform, the animals were studied as previously.[3] The results showed that the daily administration of sulfapyridine no longer caused an increase in the glucuronic acid output during the first 4 days of the experiment. After this time the

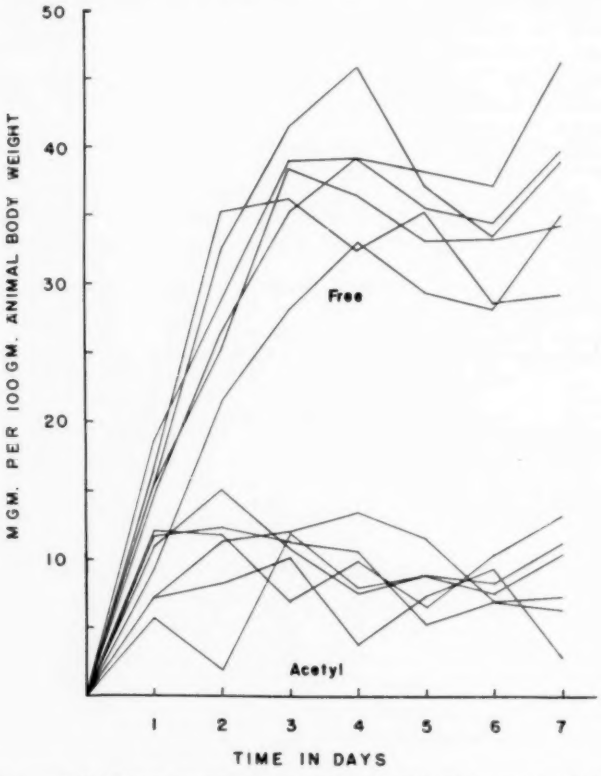

CHART. 1.—The daily urinary output of free and acetyl-sulfapyridine following the administration of 1 gm. of the drug per kilo. body weight of rat. Each line represents the results obtained with a group of 3 rats.

output began to show an upward trend, indicating a restoration of liver function. This is an agreement with the findings of Bueding and Ladewig[4] who observed histologic evidences of liver regeneration following chloroform poisoning.

More severe and lasting liver damage was then produced in 12 rats by the subcutaneous injection of 0.75 mg. of yellow phosphorus in olive oil per 200 gm. of rat. These rats were fed 3 times daily by stomach tube. Body weights remained constant throughout the

test period. Water intake and urine volume did not deviate from the normal. The daily output of glucuronic acid remained essentially unchanged, and was not stimulated by the daily administration of 1 gm. of sulfapyridine per kilo. body weight. In 9 rats the output of free and acetylsulfapyridine was essentially equivalent to that observed in animals not treated with phosphorus. In 3 rats, however, the free and acetylsulfapyridine output was markedly depressed, but extensive concretions of acetylsulfapyridine were found in the kidneys of these animals whereas none were found at autopsy in the other 9.

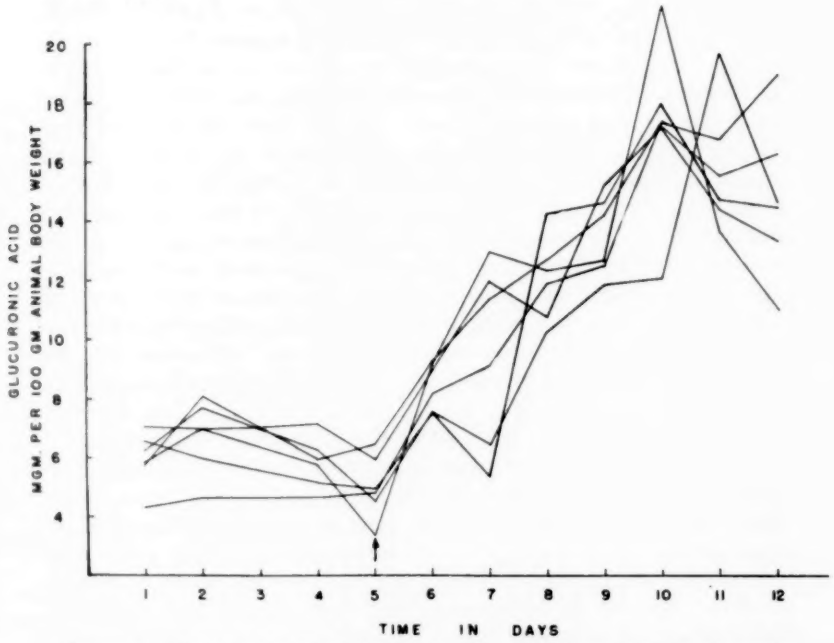

CHART 2.—The daily output of glucuronic acid. Each line represents the results obtained with a group of 3 rats. One gram of sulfapyridine per kilo. body weight was administered on the 5th and each succeeding day.

In order to decide if a still more severe liver damage would increase the incidence of urolithiasis, 20 rats were subcutaneously injected with 0.75 mg. of yellow phosphorus in olive oil, daily for 3 days. The animals were given 1 gm. of sulfapyridine per kilo. per day for 10 days and food and water were given *ad libitum*. Necropsy at the end of this time showed a 60% incidence of acetylsulfapyridine uroliths. These concretions contained 3.5% of the sulfapyridine in an unacetylated form. Thus, the stones are like those obtained without phosphorus poisoning. At this dose level only a 10% incidence of stones was found in a control series of 30 animals which were not treated with phosphorus. A 25% incidence was observed

in the series of 12 rats, mentioned above, following a single injection of phosphorus.

Discussion. It appears that the following steps, at least, are involved in the detoxication and urinary excretion of sulfapyridine. Sulfapyridine is, in part:

1. Excreted unchanged.
2. Rapidly acetylated in the liver and excreted as acetylsulfapyridine.
3. Oxidized in the liver to a hydroxysulfapyridine, some of which appears in the urine.
4. Conjugated with glucuronic acid in the liver after oxidation to hydroxysulfapyridine. This soluble product appears in urine.

Klein and Harris[8] have studied the acetylation of sulfanilamide by the liver. Sulfapyridine is acetylated by cat liver and spleen (van Winkle and Cutting[19]). In the rat this detoxication is a relatively rapid reaction, since at a fixed dose level the daily output of acetylsulfapyridine reaches its maximum within the first 24 hours (Chart 2). On the other hand, excretion of the hydroxysulfapyridine glucuronide is a two-step procedure, requiring oxidation to the phenol and subsequent conjugation. In agreement with the findings of Lipschitz and Bueding,[9] we find this over-all reaction (Chart 1) to be slow. At the present time our method* for the determination of the hydroxysulfapyridine is not sufficiently precise to permit a decision as to which of these steps is the rate controlling reaction.

Harris and Michel[7] noted a difference in the time of occurrence of sulfanilamide and methemoglobin maxima in the blood and concluded that this lag in methemoglobin formation was "due to the time necessary for the formation and accumulation of sufficient quantities of the active agent." Comparison of Figures 1 and 2 in the present study shows that maximal free sulfapyridine output occurs on the 4th day following the initiation of sulfapyridine administration, whereas maximal glucuronic acid output occurs on the 5th and 6th days. This lag can be explained on the basis of a preliminary oxidation of the drug to the hydroxysulfapyridine. That such a reaction may occur in the liver was indicated by Harris[6] and by our studies of liver damage. After the hydroxysulfapyridine is formed, it is then conjugated in the liver (Lipschitz and Bueding,[9]) and excreted by way of the urinary tract as the highly soluble hydroxysulfapyridine glucuronate.

In the absence of an accurate method for the determination of free and conjugated hydroxysulfapyridine, no precise estimate of the amounts of these substances present in urine can be given. There can be no doubt, however, that these substances do occur in rat urine in appreciable amounts. If one may assume that the increased urinary glucuronic acid is bound to a hydroxysulfapyridine, then

* This method involves an indophenol reaction similar to that used in the determination of vitamin B_6 (Scudi, Koones and Keresztesy[15]).

from stoichiometric considerations, as much as 40% of the "free" sulfapyridine may be excreted in urine in a soluble form.

Any means which may be employed to increase the percentage of the drug excreted in a water-soluble form should decrease the probability of urolithiasis. On the other hand, any dysfunction which appreciably decreases the percentage of the drug excreted in a soluble form may augment the possibility of urinary concretions; for example, in the present study phosphorus damage of the liver did not appreciably impair the ability of this organ to acetylate the drug, but it did inhibit the chain of reactions yielding the soluble product. The ability of the liver to conjugate the drug in a soluble form would therefore appear to be important. It may be desirable to test this function when occasion permits, and when prolonged sulfapyridine therapy is contemplated.

Summary. The urinary excretion of sulfapyridine has been studied in the rat. It has been shown that the drug augments the glucuronic acid output. Considering previous isolation studies in the dog, it is assumed that this indicates an *in vivo* oxidation of the drug to a monohydroxysulfapyridine with subsequent conjugation of glucuronic acid.

At the dose level used, it is estimated that as much as 40% of the free sulfapyridine may be present in the form of a highly soluble glucuronate.

Sulfanilamide does not stimulate the glucuronic acid output; sulfathiazole is intermediate between sulfanilamide and sulfapyridine in this respect.

Liver damage by phosphorus poisoning has been shown to prevent the increase in glucuronic acid output following sulfapyridine administration. The incidence of uroliths has been increased from 10 to 60% by phosphorus poisoning. Thus, in the rat the damaged liver is an important etiologic factor in urolithiasis.

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SULFATHIAZOLE IN THE TREATMENT OF PNEUMONIA IN INFANTS AND CHILDREN.*

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Since sulfathiazole—the thiazole analogue of sulfapyridine—has recently been offered to the medical profession, the authors have felt that their experiences with drug in the treatment of pneumonia in infants and children should be recorded at this time. In doing this, no attempt will be made to review in detail the comprehensive chemical, bacteriologic, pharmacologic, chemotherapeutic and clinical studies which have already been published. These investigations have revealed that sulfathiazole is rapidly and regularly absorbed from the gastro-intestinal tract. Once absorbed, the drug is not conjugated (acetylated) as much as sulfapyridine, thus permitting a large proportion of it to be therapeutically active. Excretion of sulfathiazole is, however, rapid and this shortens the period of therapeutic efficiency. Nevertheless, the drug can be given often enough so that there is a pronounced and satisfactory influence on infections due to staphylococci and pneumococci.

Table 1.—Location of the Pneumonia in the 77 Patients Treated With Sulfathiazole.

Part of lung involved.	No. of cases.
Right lower lobe	29
Left lower lobe	18
Right upper lobe	16
Left upper lobe	2
Right middle lobe	1
Left parahilar	4
Right parahilar	1
Left broncho-pneumonia (pneumococcus infection)	2
Bilateral pneumonia	3
Right upper and lower lobe	1
	77

In order to establish a dosage schedule for infants and older children, most of the patients admitted to the Pediatric Service of this hospital with a diagnosis of pneumonia were given sulfathiazole. Since the drug is poorly soluble it was administered by the oral route. During the 6-month period from January to July, 1940, 77 cases were observed. The diagnosis of the lung infection was made on the basis of a complete history, physical examination and roentgenogram study. The latter was a part of the admission procedure. Many of the patients came into the hospital close to

* Sulfathiazole was supplied by the Winthrop Chemical Company, Inc., New York.

the onset of disease. Twenty-seven cases had no physical findings over the chest at the time of admission. In these instances, the roentgenograms revealed very clearly the pneumonia. The distribution of the pulmonary involvement in our 77 children appears in Table 1, p. 718.

Before the sulfathiazole was administered the urine and blood of each patient was examined. This was followed by the bacteriologic study. An attempt was made to type all the cases employing the Neufeld method whenever pneumococci were found. Sputum specimens were usually obtained by aspiration with a bulb. When any difficulty occurred with this procedure, gastric specimens were used for typing. Occasionally, the latter specimens were so contaminated that the typing was not satisfactory. The distribution of the pneumococcus types among the patients treated with sulfathiazole is revealed in the following table:

TABLE 2.—THE PNEUMOCOCCUS TYPES IN THE 77 INFANTS AND CHILDREN WHO RECEIVED SULFATHIAZOLE.

Types.	No. of cases for each age period.					
	Below 1 yr.	1–3 yrs. (incl.).	4–6 yrs. (incl.).	7–9 yrs. (incl.).	10–12 yrs. (incl.).	Total.
Mixed types:						
V, XIV					1	1
I, XXXII			1			1
I, XVI, XVIII, XIX			1			1
VII, XX, XXIV			1			1
III, XVII		1				1
V, X		1				1
Single types:						
I	1	1	3	2	2	9
III		2	2			4
V		1	1	4	1	7
VI		3		2		5
VII			3	2		5
VIII				1	2	3
XIV	1	1	3		1	6
XVI	1	2				3
XIX	2	2	1			5
XX	2					2
XXI		2				2
Untyped	3	2	9	3	3	20
						77

Various doses of sulfathiazole were tried. The first group of cases of pneumonia received 2 to 3 gr. of the drug per pound of body weight (0.3 to 0.45 gm. per kilo) a day in divided doses for a period of 24 to 48 hours or until the temperatures dropped to normal; then the dose was reduced to 1½ gr. per pound (0.22 gm. per kilo) and continued until the patients were free of fever for 72 hours. This usually required 3 to 5 days of drug therapy.

A subsequent group of children was given 1½ gr. of the sulfathiazole per pound of body weight (0.22 gm. per kilo) a day in divided doses for the first 48 hours and then with a drop in the temperatures to

normal, this dose was reduced to 1 gr. per pound (0.15 gm. per kilo). Five to 7 days later the drug was discontinued. Since it now appeared that a dose of 1 gr. per pound per day might take care of the majority of the pneumococcus pneumonias in infants and children, the next series of cases admitted to the hospital received this dose. It was administered in divided doses, or every 4 hours, 6 times in 24 hours, and continued without any reduction until the temperature had been normal for 3 days. The total period of drug therapy was 5 to 6 days.

All ages were fairly well represented in each of the groups as will be noted in the following table:

TABLE 3.—VARIOUS AMOUNTS OF SULFATHIAZOLE EMPLOYED IN THE TREATMENT OF THE CHILDREN WITH PNEUMONIA.

Total dose per day based on body weight.	No. of cases for each age period.					
	Below 1 yr.	1–3 yrs. (incl.).	4–6 yrs. (incl.).	7–9 yrs. (incl.).	10–12 yrs. (incl.).	Total.
2–3 gr. per lb. (0.3–0.45 gm. per kilo)	3	11	8	5	2	29
1½ gr. per lb. (0.22 gm. per kilo.)	3	3	5	3	2	16
1 gr. per lb. (0.15 gm. per kilo.)	4	4	12	6	6	32
						77

The patients were closely observed once the administration of the sulfathiazole had been started. Physical examinations were frequently made. After 48 hours of drug therapy or at the time of the first evidence of a critical fall in temperature, blood was drawn for a morphologic study and for a determination of the free sulfathiazole content. Roentgenograms were also taken. The whole procedure was usually repeated on the first day of normal temperature and again on the last day of the drug therapy. Repeated urinalysis were made on all the patients.

The response to the sulfathiazole therapy was most encouraging. The children took the drug well. Although there were a few instances of nausea, there was no vomiting. The drug was administered to infants by giving the powder produced from crushing tablets, with fruit juice or milk and feeding by a teaspoon, and to children by the same method, or by giving the tablet whole with small quantities of sweetened fluids. Occasionally liquids were not satisfactory, and in these cases foods such as flavored gelatin, sweetened fruit sauces, mashed banana, simple desserts or cereal with plenty of sugar were employed.

Twenty-nine children received an initial dose of 2 gr. or more per pound of body weight per day of the sulfathiazole. Within 24 hours after the drug was started, 21 (72% of the cases) had a critical drop in temperature and 17 (60% of the patients) had a normal temperature. At the end of 48 hours, all but 1 of the children had had a critical fall in temperature and 27 (93%) had a normal temperature

(Table 4). The free sulfathiazole level of the blood determined by the method of Bratton and Marshall ranged between 10 and 15.3 mg. per 100 cc. (Table 5).

Sixteen were given an initial dose of 1½ gr. of the drug per pound of body weight per day. At the end of 24 hours, 9 (56%) of the patients had a critical drop in temperature and 8 (50%) of the cases had a normal temperature. Within 48 hours after the sulfathiazole was started, the fever had disappeared in all of the children (Table 4). The level of the drug in the free state in the blood varied from 3.7 to 14.1 mg. per 100 cc. (Table 5).

Thirty-two children received an initial dose of 1 gr. of the sulfathiazole per pound of body weight per day and this dosage was not decreased at any time during the period of drug administration. Within 24 hours after the drug was started, 23 (72%) of the cases had a critical fall in temperature and 17 (53%) of the patients had a normal temperature. At the end of the 48-hour period, 30 children had had their critical drop in temperature and 27 (85%) had a normal temperature (Table 4). The level of the drug in the free state in the blood varied from 4.6 to 10.3 mg. per 100 cc. (Table 5). Usually the pulse and respiration rates came down to normal figures shortly after the drop in temperature.

TABLE 4.—THE EFFECT OF SULFATHIAZOLE THERAPY ON TEMPERATURE.

	The various total doses per day based on body weight.					
	2–3 gr. per lb. (0.3–0.45 gm. per kilo.).		1½ gr. per lb. (0.22 gm. per kilo.).		1 gr. per lb. (0.15 gm. per kilo.).	
	No.	%.	No.	%.	No.	%.
Critical fall in temperature:						
Within 24 hours	21	72	9	56	23	72
Up to 48 hours	28	96	16	100	30	94
At end of 72 hours	29	100			32	100
Temperature at normal level:						
Within 24 hours	17	60	8	50	17	53
Up to 48 hours	27	93	16	100	27	85
At end of 72 hours	29	100			32	100
Secondary rise in temperature in 10 children (13%)	3	4	2	3	5	6

TABLE 5.—AMOUNT OF FREE SULFATHIAZOLE IN THE BLOOD AS DETERMINED BY THE METHOD OF BRATTON AND MARSHALL.

Total dose per day based on body weight.	No. of cases.	Range of drug in mg. per 100 cc.
2–3 gr. per lb. (0.3–0.45 gm. per kilo.)	29	10.0 to 15.3
1½ gr. per lb. (0.22 gm. per kilo.)	16	3.7 to 14.1
1 gr. per lb. (0.15 gm. per kilo.)	32	4.6 to 10.3

The drug was administered every 3 or 4 hours throughout the day and night. Some of the children received soda bicarbonate with each dose of the sulfathiazole but the majority did not. Two children who were considered to be in acidosis at the time of admission to the hospital were given fairly large amounts of the alkali. Sedatives and cough mixtures were occasionally permitted. Serum therapy was not employed in any case.

The careful clinical observations of the patients together with the frequent roentgenogram examinations revealed that the resolution of the pneumonic infection began about the third or fourth day, was usually under way to a fair degree by the fourth or fifth day, was quite well advanced by the fifth to the sixth day, and in some cases completed by the seventh to eighth day. The critical drop in temperature preceded the beginning of resolution by 12 to 24 hours. Ten children (13%) had a secondary rise in temperature following the initial fall. In these children, resolution did not begin until the temperature had finally returned to normal.

No evidence of urinary disturbance was detected in any of the patients. The most disturbing feature of the chemotherapy was the appearance of a drop in the polymorphonuclear blood cells. This occurred in 10 cases listed in Table 6 beginning usually after the sulfathiazole had been administered for 48 hours and continued for 3 to 5 days. With a discontinuance of the drug, the white blood cells immediately began to rise, often reaching the normal figure in 7 days. No instance of a serious blood change was noted.

TABLE 6.—THE 10 CASES REVEALING ACUTE LEUKOPENIA WITH GRANULOCYTOPENIA.

	Dose per day based on weight.		Actual amt. of drug received by each patient.		Admission counts.		Subsequent counts.	
Age.	Gr. per lb.	Gm. per kilo.	Gr.	Gm.	White blood cell.*	Pmn. diff.†	White blood cell.*	Pmn. diff.†
3 yrs.	2	0.30	255	17	20000	80	5350	39
6 yrs.	2	0.30	390	26	20090	80	6000	20
8 mos.	1½	0.22	225	15	13000	50	5350	11
13 mos.	1½	0.22	153	10	12350	50	9850	20
3 yrs.	1½	0.22	225	15	9450	79	5500	29
3 yrs.	1½	0.22	150	10	7000	43	8800	31
3 yrs.	1½	0.22	142	9	6500	71	6450	29
4 yrs.	1½	0.22	262	17	29750	79	6102	29
9 yrs.	1½	0.22	626	42	6450	..	3400	35
5 yrs.	1	0.15	240	16	19850	85	4200	40

* Total white blood corpuscle count.

† Polymorphonuclear cell count based on 300 cells and expressed in %.

The incidence of complications was small. There was 1 case which developed empyema and another was found to have a lung abscess. The progress in each of these children was good. There were no deaths—all of the 77 children with type specific pneumococcus pneumonia or lobar pneumonia with negative typing receiving the sulfathiazole survived. These results equaled those of sulfapyridine and certainly surpassed those of specific serum therapy as may be observed in Table 7, p. 723.

Incidently, the poor showing of the serum-treated cases was due to an insufficient dose of the specific serum, mistakes in typing, or infection by more than one type of the pneumococcus.

Sulfathiazole compares favorably with sulfapyridine. The latter drug acts faster as evidenced by the critical fall in temperature within 24 hours, although at the end of 48 hours the effect of both

drugs on the temperature was practically the same. Much of the nausea and vomiting which occurred frequently with the administration of sulfapyridine was absent when sulfathiazole was given. In fact, we had few untoward effects from the sulfathiazole. There was no vertigo, headache, and malaise. Fever and cutaneous eruptions were not observed, although these side effects have been seen by some investigators. Hematuria and anuria were not present. There was no evidence in any case of injury to nerve tissue. However, acute leukopenia with granulocytopenia did occur and cleared up soon after the sulfathiazole had been discontinued.

TABLE 7.—RESULTS OF THE TREATMENT OF PNEUMONIA (PNEUMOCOCCUS OR LOBAR) IN INFANTS AND CHILDREN AT THE MINNEAPOLIS GENERAL HOSPITAL DURING A CORRESPONDING PERIOD (JANUARY TO JULY) OF EACH YEAR.

Year.	No. of cases.	Treatment.	No. of cases of empyema.	% of empyema.	No. of deaths.	Mortality rate.
1933	69	No specific therapy	1	1.44	11	15.94
1934	75	No specific therapy	14	18.66	5	6.66
1935	86	No specific therapy	15	17.44	6	6.97
1936	138	Serum	14	10.14	9	6.52
1937	82	Serum	6	7.31	4	4.87
1938	68	Serum	2	2.94	10	14.70
1939	65	Sulfapyridine	3	4.61		
1940	77	Sulfathiazole	1	1.29		

We recommend sulfathiazole for the treatment of pneumonia in infants and children, although each patient must be closely watched for toxic reactions. Various amounts of the drug have been tried and it was found that 1 gr. per pound (0.15 gm. per kilo) was effective but that 1½ gr. or even 2 gr. could be administered without any serious untoward effects. Sulfathiazole is supplied in tablets of 0.5 gm. (7.72 gr.) and also in tablets of 0.25 gm. (3.86 gr.). Although it would be ideal to determine the dosage requirements in the metric system, that is, the number of grams per kilogram per day, many practising physicians prefer to know the number of tablets necessary for each dose based chiefly on the age of the patient. For their convenience may we present the following schedule in which the doses are calculated on the basis of 1 to 1½ gr. per pound (0.15 to 0.22 gm. per kilo) of average body weight per day. The sulfathiazole should be administered without any reduction every 4 hours, 6 times in 24 hours, until the temperature has been normal for 3 days. This usually requires a total of 5 to 6 days of drug therapy. Further investigations which are now in progress may alter this dosage recommendation.

Age.	Single dose (gr.).	Tablets. 0.25 gm.	Tablets. 0.50 gm.	Interval (hrs.).	Total 24-hr. dose (gr.).
Below 6 mos.	1.93	½	¼	4	11.58
6 mos.–1 yr.	3.86	1	½	4	23.16
1–3 yrs. (incl.)	5.79	1½	¾	4	34.74
4–6 yrs. (incl.)	7.72	2	1	4	46.32
7–9 yrs. (incl.)	11.58	3	1½	4	69.48
10–12 yrs. (incl.)	15.44	4	2	4	92.64

Summary. Seventy-seven of the infants and children admitted to the Pediatric Service of the Minneapolis General Hospital from January to July, 1940, with a diagnosis of pneumonia were given sulfathiazole—the thiazole analogue of sulfapyridine.

An attempt was made to type all of the cases by the Neufeld method. In many of the patients this procedure gave positive results revealing a fairly good distribution of the pneumococcus types. The remainder of the children who gave a negative or unsatisfactory Neufeld test did, however, have a lobar type of pneumonia.

Various doses of the sulfathiazole were tried and in doing this all ages of the children were fairly well represented.

The response to the sulfathiazole therapy was most encouraging. The patients took the drug well. There was little of the nausea and vomiting frequently encountered with sulfapyridine.

Toxic manifestations were few in number. The most disturbing feature of the chemotherapy was the appearance of a drop in the polymorphonuclear blood cells. With a discontinuance of the drug, the white blood cells soon returned to the normal figure.

Careful clinical observations of the patients receiving the various amounts of the sulfathiazole together with the determinations of the level of the drug in the free state in the blood permitted a dosage schedule to be established. It is presented with the understanding that although this will be of value to the practising physician at the present time, future clinical studies may produce changes which will give even better results.

THE DISTRIBUTION OF SULFANILAMIDE BETWEEN BLOOD AND CEREBROSPINAL FLUID WITH SPECIAL REFERENCE TO INTRASPINAL TREATMENT.

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Sulfanilamide compounds have been the subject of numerous comprehensive pharmacologic and pharmacodynamic studies. The special aspect of the passage of sulfanilamide from the general circulation into the cerebrospinal fluid has, however, received only

scant attention. Yet, such study deserves serious consideration for what it may contribute to our present knowledge of both the mode of action of the drug and its rational mode of administration in certain pathologic conditions.

The use of sulfanilamide in diseases of the cerebrospinal nervous system brings forward once more the much debated problem of whether or not it is necessary for a drug present in the general circulation to pass into the cerebrospinal fluid in order to affect the cerebrospinal nervous system. If it were satisfactorily proven that sulfanilamide passes from the blood into the cerebrospinal fluid (C.S.F.) rapidly and in relatively high concentrations there would be no indication for intraspinal administration of the drug. This would be recognized even by those investigators who feel that substances introduced into the blood reach the cerebrospinal nerve tissues *via* the C.S.F.[6]

Both clinical and laboratory studies have dealt with the subject here considered. Sulfanilamide has been recovered in the C.S.F. in man 4 to 5 hours after administration of the drug by mouth.[7] In cases of meningitis in men marked differences were found between prontosil B (base) and prontosil S (soluble), with regard to their passage from the general circulation into the C.S.F. In a case of severe purulent meningitis it took 2 days before the daily dose of 1.8 gm. of prontosil B was found in the C.S.F. In the same patient prontosil S was detected the next day. On the other hand, in a case of mild meningitis neither prontosil B nor prontosil S could be detected in the C.S.F. after the oral administration of the former and the intramuscular administration of the latter. In another case of mild meningitis prontosil B given orally was not found in the C.S.F., whereas prontosil S given intramuscularly passed into the C.S.F.[4] The content of sulfanilamide in the C.S.F. was found to vary considerably (1.2 to 17.8 mg. per 100 cc.) in 6 patients and not to bear any relation to the course of the disease or to the rapidity of sterilization of the fluid. Yet, experience suggests to the authors that the intraspinal way may prove to be a very efficient way of giving the drug.[3] Sulfanilamide concentration proved to be similar in blood and C.S.F. "the first hours" after the administration of the drug. But during the "early hours" in the phase of ascent of the sulfanilamide content in blood and C.S.F. it was higher in the former than in the latter. The reverse was observed to $1\frac{1}{2}$ to $2\frac{1}{2}$ days after the onset of medication.[1] Because of differences in procedure, this study does not lend itself well for an analysis of the blood-C.S.F. sulfanilamide relationship. Malaria treatment has proven to favor the passage of prontosil from blood into C.S.F. Thus, in patients who received the treatment, prontosil permeated into the C.S.F., the amount being directly correlated with the globulin content of the C.S.F. On the other hand, in

patients without malaria treatment, prontosil was not found in the C.S.F.[8] In patients with "intact" blood-C.S.F. barrier, examinations of blood and C.S.F. at hourly intervals and for 5 hours after the oral or parenteral administration of various sulfanilamides revealed the following results: Soluble prontosil given orally could not be detected in the C.S.F. Sodium sulfanilate in solution entered only in very small amounts; prontosil album showed the highest permeation. The latter was practically nil for dimethyl-disulfanilamide.[9]

Experimental studies showed that 30 minutes after the intravenous injection of prontosil S (2 cc. of 2.5% solution per kilo body weight) to normal rabbits only slight traces of the drug were found in the C.S.F. On the other hand, in 9 rabbits with artificially provoked acute or chronic meningitis—under otherwise similar experimental conditions—the concentration of the drug in the C.S.F. ranged between 0.374 and 1.140 mg. per 100 cc.[5]

Our own studies were carried out in 31 patients of this hospital. One common feature in all of them is the normal findings—protein, cells, and serologic reactions—in the cerebrospinal fluid. Otherwise, the patients may be divided into two groups: *A*, Patients with diagnosis of schizophrenia in whom both general physical and special neurologic examinations did not reveal any abnormal findings. *B*, Patients who in addition to their psychotic disorders are afflicted with varied organic diseases.

For the determination of sulfanilamide in blood and C.S.F. the method of Bratton and Marshall was used.[2]

A. **Psychotic Patients With No Physical Disease.** The 16 schizophrenic patients, from 26 to 42 years of age, were subdivided into two groups.

Group 1 (9 Patients): Each patient received by mouth therapeutic doses of sulfanilamide, namely, 25 grains every 6 hours—plus sodium bicarbonate 15 grains—a total of 100 grains in 24 hours. The medication was discontinued at the end of the third day.

Sulfanilamide* was analyzed in specimens of blood and C.S.F. obtained at the same time. Twenty-four hours after the beginning of the treatment, each of the patients having received 100 grains of sulfanilamide, the blood content of the latter varied from 4.26 to 8 mg. per 100 cc.; the spinal fluid content from 3.92 to 6.67 mg. per 100 cc.; and the permeability quotient $\left(\frac{\text{blood sulfanilamide}}{\text{C.S.F. sulfanilamide}}\right)$ from 1.1 to 1.68. At the end of 3 days' treatment, with a total of 300 grains, blood sulfanilamide values ranged from 6.25 to 8.6 mg. per 100 cc.; spinal fluid values from 5.06 to 7.6 mg. per 100 cc., and permeability quotient from 1.1 to 1.36. Twenty-four hours following the discontinuation of sulfanilamide its content varied in blood from 1.76 to 3.43 mg. per 100 cc., and in spinal fluid from 1.29 to

* Free sulfanilamide.

3.2 mg. per 100 cc., and the permeability quotients were between 1.35 and 1.88.

Group 2 (7 Patients): These patients also received 100 grains of sulfanilamide per day, in 4 equal doses, during 3 consecutive days; sodium bicarbonate was given with each dose of sulfanilamide. The difference in procedure, as compared to Group 1, consisted in extension of the analyses of sulfanilamide to 48 hours after cessation of the medication. Twenty-four hours after beginning of the treatment sulfanilamide ranged in blood from 4.7 to 8.0 mg. per 100 cc., and in spinal fluid from 3.35 to 5.92 mg. per 100 cc.; the permeability quotient varied from 1.06 to 1.59. The second day of the treatment, the blood level fluctuated from 6.15 to 10.88 mg. per 100 cc., the C.S.F. level from 4.52 to 8.25 mg. per 100 cc., and the permeability quotient from 1.17 to 1.44. On the third day of medication, the concentration in blood was between 6.06 and 12.31 mg. per 100 cc., and in C.S.F. between 4.5 and 10.13 mg. per 100 cc.; the permeability quotients were between 1.19 and 1.34.

Twenty-four hours after treatment was discontinued, blood sulfanilamide ranged from 2.0 to 5.8 mg. per 100 cc.; cerebrospinal fluid sulfanilamide from 1.5 to 4.94 mg. per 100 cc., and the permeability quotients from 1.12 to 1.5. Forty-eight hours after discontinuation of medication, sulfanilamide ranged from 0.66 to 3.0 mg. per 100 cc., in blood and from a trace to 2.73 mg. per 100 cc. in C.S.F., the permeability quotient in those cases in which the C.S.F. contained measurable amounts of sulfanilamide ranged from 1.09 to 1.2.

B. **Psychotic Patients With Physical Diseases.** Again, differences in procedure lead us to subdivide the 15 patients into three groups (3, 4, 5).

Group 3 (5 Patients Above 50 Years of Age): In addition to the psychiatric diagnosis of schizophrenia, the physical diagnoses were arteriosclerosis in 4 cases and cerebral lues in 1 case. These patients were also given 100 grains of sulfanilamide per day in divided doses. The essential difference in procedure lies in a more marked prolongation of medication in 4 cases, and in extension of analyses of sulfanilamide after cessation of medication in all 5 cases. The main interest in these 5 patients is centered, however, not so much on the sulfanilamide values during medication but rather on the behavior of the drug after cessation of the medication:

Thus, in 1 case (Al.) in which sulfanilamide was given for 3 days but analyses of the drug were followed for 5 days after its discontinuation the results were as follows: On the 1st day, sulfanilamide concentration dropped from 13.4 to 6.72 mg. per 100 cc. in blood, and from 9.75 to 6.61 mg. per 100 cc. in C.S.F.; the permeability quotient changed from 1.38 to 1.01. On the 2d day the blood content was 3.64 and the C.S.F. content 3.92 mg. per 100 cc.; the permeability quotient went down to 0.92. On the 3d day no sulfanilamide could be found in the blood, but 0.45 mg. per 100 cc. was still

present in the C.S.F. Tests on the 4th and 5th days, following cessation of medication, showed no traces of the drug in either blood or C.S.F.

Four patients were given sulfanilamide for 5 days, each receiving a total of 500 grains. Inasmuch as sulfanilamide in both blood and C.S.F. followed a similar trend in all the 4 cases, the findings in 1 case (Cr.) only are recorded: Two days after discontinuing treatment, sulfanilamide had fallen in blood from 14.54 to 3.48 mg. per 100 cc., and in C.S.F. from 12.3 to 5.92 mg. per 100 cc.; the permeability quotient changed from 1.18 to 0.58. Three days after cessation of medication sulfanilamide was 2.82 in blood and 3.48 mg. per 100 cc. in C.S.F.; the permeability quotient was still 0.81. Four days after completion of treatment, sulfanilamide in blood was 2.08 and in spinal fluid 1.92 mg. per 100 cc.; the permeability quotient rose to 1.08.

Thus, the cases of this group show that after medication with sulfanilamide at the rate of 100 grains per day for 5 days considerable quantities of the drug persist in the blood and spinal fluid as long as 4 days after discontinuation of the treatment.

Group 4 (*5 Psychotic Patients With General Arteriosclerosis*). In these patients the behavior of sulfanilamide in blood and C.S.F. was followed after a single dose (2 gm.) was given. Four hours after its administration, sulfamilamide in blood varied from 0.12 to 0.41, and in C.S.F. from 0.9 to 0.23 mg. per 100 cc.; the permeability quotient showed a wide variation, from 1.33 to 2.92. Twenty-eight hours later, sulfanilamide ranged in blood from 0.1 to 0.14 and in C.S.F. from 0.14 to 0.18 mg. per 100 cc.; the permeability quotient varied from 0.71 to 0.87.

Group 5 (*5 Psychotic Patients With Organic Diseases*). Paget's disease, 2 cases; arteriosclerosis, 2 cases; epilepsy-chorea, 1 case. As in Group 4, the patients received a single, but higher dose—5 gm.—of sulfanilamide. Four hours after the drug was given, its content in blood ranged from 3.41 to 7.7 and in C.S.F. from 1.68 to 4.13 mg. per 100 cc.; the permeability quotient varied from 1.87 to 2.33. Twenty-eight hours after administration of the drug, its concentration in blood was between 1.23 and 3.22 and in C.S.F. between 1.29 and 2.51 mg. per 100 cc.; the permeability quotients ranged from 0.84 to 1.23.

Comment. The outstanding feature in all our results is the passage of sulfanilamide from blood into C.S.F. in considerable concentrations, as compared to those in blood. This is readily seen in the permeability quotients $\left(\frac{\text{blood sulfanilamide}}{\text{C.S.F. sulfanilamide}}\right)$: Thus, in the 16 schizophrenic patients without organic disorders (Groups 1 and 2), the permeability quotients vary from 1.06 to 1.68 at the end of the 1st day of medication, from 1.17 to 1.44 at the end of the 2d day, and from 1.19 to 1.36 at the end of the 3d day of treatment.

In the 10 patients (Group 4 and 5) who received single doses (2 or 5 gm.) of sulfanilamide, the permeability quotients range between 1.33 and 2.92 four hours after administration of the drug, and between 0.71 and 1.23 twenty-eight hours after the drug was given. This considerable lowering of the permeability quotients suggests that after cessation of medication, blood loses sulfanilamide at a higher rate than the C.S.F. does. This suggestion becomes well-nigh a certainty when one considers the sulfanilamide values obtained within several days after cessation of treatment of 3 to 5 days' duration. Thus, the findings in the 2 illustrating cases (Al. and Cr.) of Group 3 demonstrate a gradual decrease of their permeability quotients during the 3 days following cessation of medication. These 2 cases also exemplify individual variations, all other conditions being similar. Thus, in Case Al. no sulfanilamide could be detected in either blood or C.S.F. 4 days after discontinuation of medication. In Case Cr. the permeability quotient rose the 4th day, and at the same time considerable concentrations of sulfanilamide were found in both blood and C.S.F. The relatively higher loss of sulfanilamide in blood than in C.S.F. admits the working, at least, of three mechanisms; namely, more rapid elimination of the drug from blood, its higher permeation from blood into C.S.F., slower penetration of the drug from C.S.F. into blood.[6] This is not the occasion to discuss the relative effectiveness of each of the respective mechanisms. For our purpose it suffices to register and reëmphasize the fact that sulfanilamide not only readily penetrates from the general circulation into the C.S.F. but that it also is being eliminated more slowly from the latter than from the former.

Conclusion. Oral administration of sulfanilamide assures the penetration of the drug into the C.S.F. in concentration sufficiently high to render unnecessary intraspinal administration of the drug. It should be noted that in our cases there were neither clinical nor laboratory findings (the C.S.F. was normal) which would suggest meningeal involvement of any moment. Yet, it is principally in meningitides that sulfanilamide has heretofore found its therapeutic usefulness, and it is also in meningitis that the passage of the drug from the blood into C.S.F. is likely to be at a higher rate than in our cases, inasmuch as in inflammatory processes of the meninges (of infectious and aseptic origin) the permeability of the barrier between blood and C.S.F. is usually increased.[6]

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FAILURE OF PARA-AMINOBENZOIC ACID TO INHIBIT SULFONAMIDE RASHES AND FEVERS.

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A NUMBER of substances have the property of inhibiting the bactericidal action of the sulfonamide drugs on various types of bacteria. Materials which exhibit this property have been isolated from bacterial cells[2,3,7] and from animal tissues.[5] These substances have not yet been chemically defined. Peptones[4] and coenzymes,[9] under certain conditions, have also been shown to inhibit the bactericidal activity of sulfonamide drugs. Woods[10] identified various fractions of yeast concerned in this action, and from an analysis of the chemical properties of the active fractions found that *p*-aminobenzoic acid exhibited a marked degree of inhibitory effect on the bactericidal action of sulfanilamide. Selbie[6] demonstrated that mice infected with hemolytic streptococci could not be saved with sulfanilamide if *p*-aminobenzoic acid were administered at the same time.

In a separate communication, we have presented data which confirm and extend some of Woods' observations.[8] Our results may be summarized briefly:

1. *In vitro*, there is a roughly linear relationship between the concentrations of sulfonamides that are bacteriostatic for pneumococci and the minimum amounts of *p*-aminobenzoic acid that inhibit that action. The inhibitory effect of *p*-aminobenzoic acid varies with the different sulfonamide compounds. For example, 0.004 mg. per 100 cc. of *p*-aminobenzoic acid inhibited the bacteriostatic effect on pneumococci of 10 mg. per 100 cc. of sulfanilamide; while 0.04 mg. per 100 cc. of *p*-aminobenzoic acid was required to overcome the action of 10 mg. per 100 cc. of sulfathiazole.

2. The action of sulfapyridine on pneumococci can be nullified at any stage short of complete killing by the addition of *p*-aminobenzoic acid. Pneumococci "revived" by this means grow like a similar number of viable organisms freshly inoculated into the same medium without sulfapyridine.

3. Para-aminobenzoic acid is readily absorbed after oral administration and is rapidly excreted in the urine. It is distributed in red

blood cells and blood plasma, though in higher concentration in the latter. The substance was administered to many subjects without untoward effects.

4. The pneumococcidal action of human blood resulting from the administration of sulfapyridine and sulfathiazole can be overcome by the oral administration of *p*-aminobenzoic acid, even though sulfonamide therapy is continued.

5. Para-aminobenzoic acid excreted in urine or added to urine *in vitro* nullifies the bactericidal action of sulfathiazole on colon bacilli.

Results of (1) and (2) have been utilized clinically in the culture of body fluids from patients receiving sulfonamide therapy.

The suggestion has been made that *p*-aminobenzoic acid might inhibit not only the bactericidal action of the sulfonamide drugs, but also their toxic effects in human tissues.[1] To test this hypothesis the studies reported here were carried out. A type of toxic reaction to the sulfonamide drugs was sought which, 1, is an objective manifestation, 2, disappears quickly on withdrawal of the offending drug and, 3, reappears if the drug is again administered. Drug fevers and rashes were selected for study because they fulfill these criteria.

An attempt was first made to overcome drug fever by the administration of *p*-aminobenzoic acid. The following cases are illustrative:

Case Reports. CASE 1.—S. L., a 17-year-old colored female, was admitted to the hospital on July 15, 1940, with gonorrheal arthritis. Beginning on the day of admission, 1 gm. of sulfathiazole was given every 4 hours for the next 3 weeks. On August 7, the patient's temperature was slightly elevated and she complained of nausea and headache. The drug was then discontinued and for the next 10 days she was afebrile. On August 15, at 9 P.M., sulfathiazole treatment was begun again and continued with a dose of 1 gm. every 4 hours for the next 28 hours. Immediately after the first dose of sulfathiazole the patient complained of nausea and headache. Within 8 hours of the first dose the rectal temperature had risen to 101° F., and thereafter remained between 100° and 102° F. until sulfathiazole was discontinued. Seventeen hours after the first dose of sulfathiazole the patient was given 2 gm. of *p*-aminobenzoic acid. This dose was repeated at 3-hour intervals for the next 12 hours. Blood taken just before the first dose of *p*-aminobenzoic acid showed moderate pneumococcidal power, while a blood sample taken after the second dose of *p*-aminobenzoic acid showed almost complete loss of this killing power. During the 12-hour period of *p*-aminobenzoic acid administration there was no amelioration of the patient's symptoms, nor was the temperature reduced. Twelve hours after the last dose of sulfathiazole the temperature was normal and the symptoms gone.

CASE 2.—L. C., a 50-year-old white male, was admitted with dysuria and fever. A diagnosis of cystitis and prostatism was made. Beginning on August 21, 1940, 1 gm. of sulfathiazole was given every 4 hours. The patient's temperature returned to normal in 3 days and his urinary symptoms disappeared. The drug therapy was continued. On August 30, the patient's temperature was elevated to 102.6° F. He was drowsy, sweating and nauseated. No rash was noted. There were no urinary symptoms.

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Sulfathiazole was continued on the same dosage schedule and, in addition, 1 gm. of *p*-aminobenzoic acid was given at 2-hour intervals for the next 8 hours. During this time the temperature rose steadily to a maximum of 104.6° F., 8 hours after the first dose of *p*-aminobenzoic acid. At this time both drugs were discontinued. The temperature reached normal 12 hours later. Blood taken before the administration of *p*-aminobenzoic acid showed marked pneumococcidal action; blood taken after *p*-aminobenzoic acid had been given showed complete loss of killing power.

In these 2 cases, therefore, once sulfonamide fever had become manifest it could not be overcome or inhibited by the administration of *p*-aminobenzoic acid. The failure to overcome the drug fever was manifest in spite of the fact that the antibacterial property of the blood attributable to the sulfonamide therapy had been overcome by the *p*-aminobenzoic acid.

Additional patients were then selected who had previously exhibited signs of toxic reactions to sulfonamides. These patients were given *p*-aminobenzoic acid during and before a second course of sulfonamide therapy in an attempt to prevent a recurrence of drug toxicity. The results in 2 such cases may be described briefly:

CASE 3.—M. T., a 31-year-old white female, was admitted to the hospital with signs of pneumonia. Sulfathiazole was begun on the second hospital day and continued for the next 7 days. The temperature fell to normal on the sixth day. On the eighth day the temperature was again elevated and on the following day rose to 103° F. At the same time a diffuse erythematous morbilliform rash appeared. The drug was discontinued, and in 20 hours the temperature fell to normal and the rash faded completely. On the tenth day, 1 gm. of *p*-aminobenzoic acid was given at 2-hour intervals. With the third dose of *p*-aminobenzoic acid a single dose of 1 gm. of sulfathiazole was given. Two hours later the rash recurred and the temperature rose, both the rash and the fever reaching their height 9 hours after administration of the single dose of sulfathiazole. Twelve hours later the temperature was normal and the rash had again disappeared. The course of events is illustrated in Figure 1.

CASE 4.—G. N., a 72-year-old white male, had been hospitalized for many weeks because of a cerebral vascular accident. He was given sulfathiazole in an attempt to clear up severe decubitus ulcers. On the sixth day of sulfathiazole therapy an "erythema nodosum" type of rash was noted. It consisted of irregularly rounded, purplish-red nodules on the extensor aspects of the knees and forearms and on the cheeks and forehead. The drug was continued for 3 days more, during which time the temperature rose to 102° F. and the rash became more extensive. Five days later, when the temperature was normal and the rash had disappeared, a single 0.5 gm. dose of sulfathiazole was given. There were no toxic reactions during the next 48 hours. Para-aminobenzoic acid was then administered at 2-hour intervals over the next 52 hours, a total dose of 29 gm. Three hours after the first dose of *p*-aminobenzoic acid, sulfathiazole was again started and 13 gm. were given in the next 48 hours. Forty hours after the first dose of sulfathiazole the rash recurred and the temperature rose to 101° F. With the omission of both drugs, rash and fever disappeared. As a control, the patient was given *p*-aminobenzoic acid, without sulfathiazole, for a total of 33 gm. over a 66-hour period. During this time there was no recurrence of rash or fever. The course of events is shown in Figure 2.

The toxic effects of sulfathiazole therapy manifested by fever and rash were neither prevented nor cured by oral administration of *p*-aminobenzoic acid.

Comment. Fildes[1] expressed the view that *p*-aminobenzoic acid may be an "essential metabolite" in animal cells. By virtue of their structural similarity with this substance, the sulfonamides are

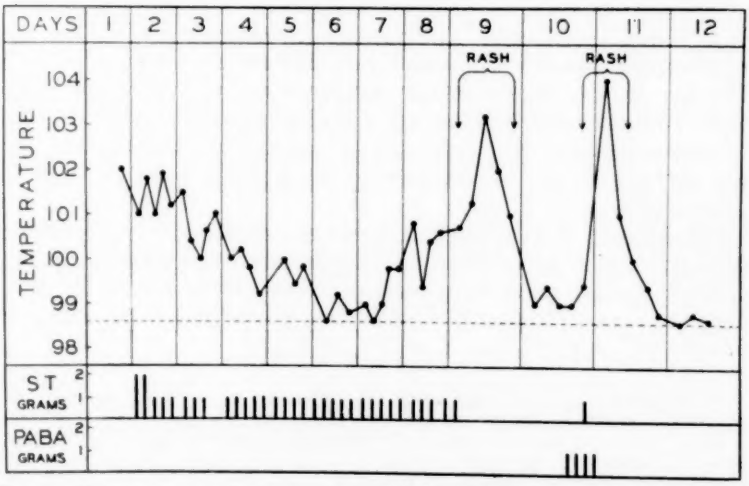

FIG. 1.—Failure to prevent recurrence of sulfathiazole (ST) rash and fever by administration of *p*-aminobenzoic acid (PABA) in Case 3.

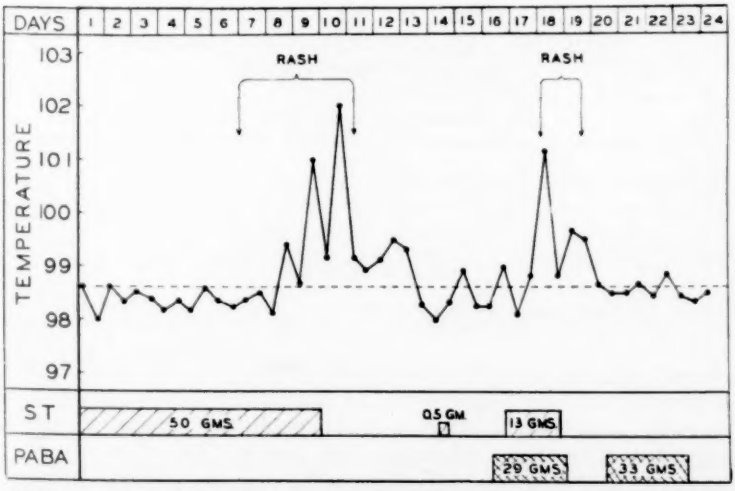

FIG. 2.—Case 4. Failure to prevent or to influence the recurrence of sulfathiazole (ST) fever and rash by administration of *p*-aminobenzoic acid (PABA) and the failure of the latter by itself to reproduce these symptoms.

thus considered to produce toxic effects in tissues by replacing *p*-aminobenzoic acid in the course of metabolic processes. Much of the data concerning the mode of action of the sulfonamides, including our studies previously summarized, are consistent with such an hypothesis in so far as it concerns bacterial growth. The present clinical observations, however, do not support this hypothesis with respect to toxic effects in human tissues.

The mechanism of the production of sulfonamide fevers and rashes is at present unknown. The various sulfonamide drugs differ not only in the frequency with which they produce these toxic reactions, but also in the variety of the cellular reactions. The possibility that *p*-aminobenzoic acid or other similar substances may prevent or overcome some other types of toxic reactions to sulfonamides has not been excluded. Investigations along these lines are still in progress.

Conclusions. Fevers and rashes due to sulfathiazole could neither be overcome nor prevented by the administration of *p*-aminobenzoic acid, even when given in amounts sufficient to overcome the antibacterial action of the sulfonamide drug in the blood and urine.

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THE MODE OF ACTION OF MAGNESIUM SULPHATE IN REDUCING THE HYPERTENSION OF ACUTE GLOMERULONEPHRITIS.*

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Since the introduction of magnesium sulphate, by Blackfan and his coworkers,[3,4] for the lowering of the elevated blood pressure in the early phase of acute glomerular nephritis, extensive clinical experience with this substance has proven its efficacy. It is commonly held that cerebral edema is the primary stimulus bringing

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about the hypertension of acute glomerulonephritis. The mechanism by which magnesium sulphate reduces this hypertension, however, has remained obscure. The generally advanced explanation for its *modus operandi* is that it is a dehydrating agent, promoting loss of water from the body with resultant cerebral dehydration.

The clinical experiments recorded here have been planned to elucidate the mode of action of magnesium sulphate in the patient with hypertension in acute glomerulonephritis, especially in relation to dehydration. The first series of observations were made to determine whether dehydration was associated with the fall in

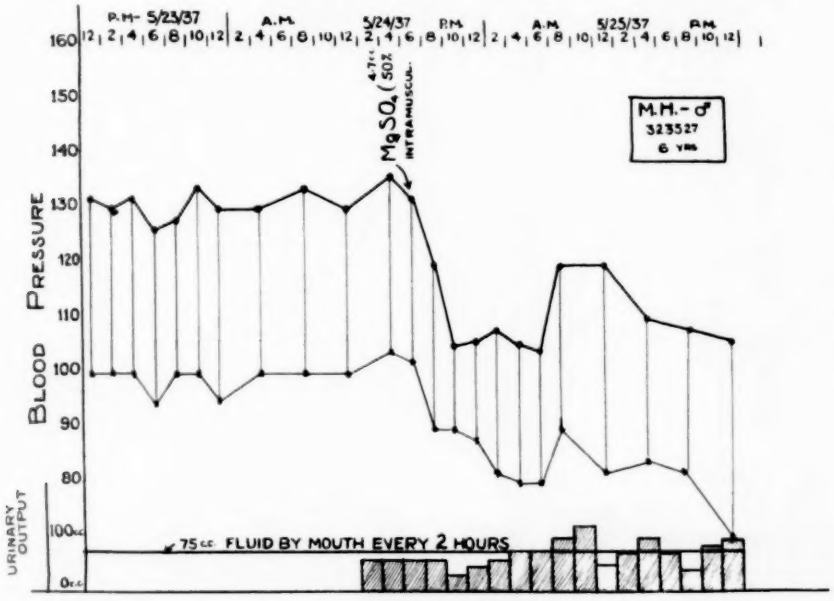

FIG. 1

blood pressure induced by magnesium sulphate given intramuscularly. Figures 1 and 2 are representative of such experiments. The patients were given fixed amounts of orange juice (75 cc.) at 2-hour intervals. Urine collections were made at these times. The blood pressure was taken at hourly periods. This régime was maintained for 12 to 24 hours before administration of magnesium sulphate, to ascertain the variability of the blood pressure. When the pressure had remained fairly stable for a period of about 6 hours, the magnesium sulphate (0.2 cc., 50% solution per kg. of body weight) was given into the muscles of the buttocks. It is apparent from the figures that there was no diuresis accompanying the fall in blood pressure. During the short period of the experiment, weight changes did not occur. It is, therefore, reasonable to conclude that

magnesium sulphate is able to lower the blood pressure without producing dehydration (loss of body water).

Approaching the problem from another viewpoint, the effect of a known dehydrating agent upon the hypertension was studied. If the original concept of magnesium action, viz., its dehydrating effect, were correct, then loss of water from the body produced by other means should be effectual in lowering the blood pressure. The intravenous administration of hypertonic sucrose (50%) was used for this purpose since it has been shown to produce dehydration, both general and cerebral.[5,9] Patients were placed on a régime

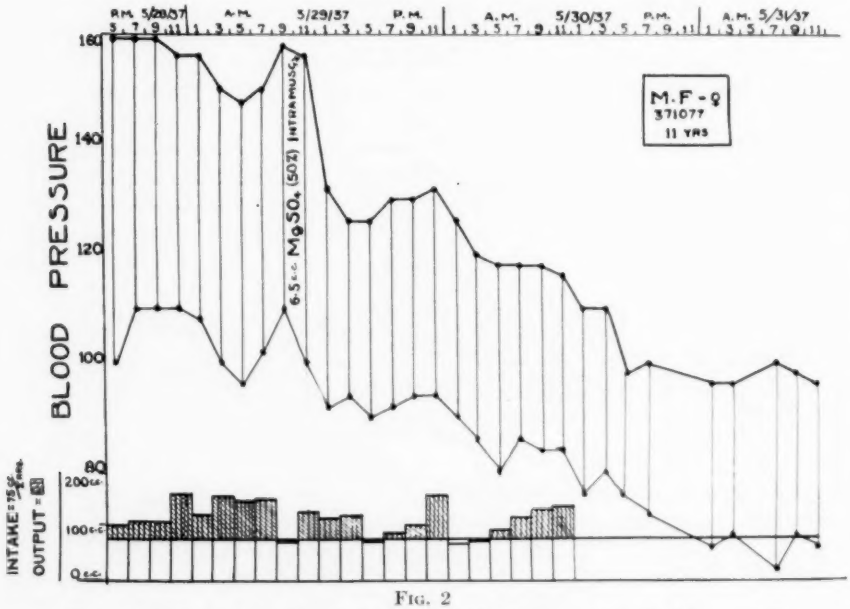

FIG. 2

FIGS. 1 and 2.—A lowering of the elevated blood pressure by the intramuscular injection of $MgSO_4$, without accompanying dehydration (*i. e.*, loss of water by diuresis).

similar to that in the magnesium experiment. Figure 3 depicts the result of one of these experiments. Following the injection of 100 cc. of 50% sucrose, free diuresis occurred. This was not followed by a fall in blood pressure.

Figure 4 represents the data obtained in a patient to whom both sucrose and magnesium were given in sequence. Following the injection of 50 cc. of hypertonic sucrose, there was diuresis with no fall in blood pressure. Fourteen hours after the sucrose administration, and while the blood pressure was still elevated, magnesium sulphate was injected. There followed a fairly rapid fall in blood pressure, with no associated diuresis. About 24 hours later, when

the blood pressure had again attained a higher level, twice the initial dose of sucrose was administered. The urinary output following this was even greater than that after the first sucrose injection, again with no effect on the blood pressure.

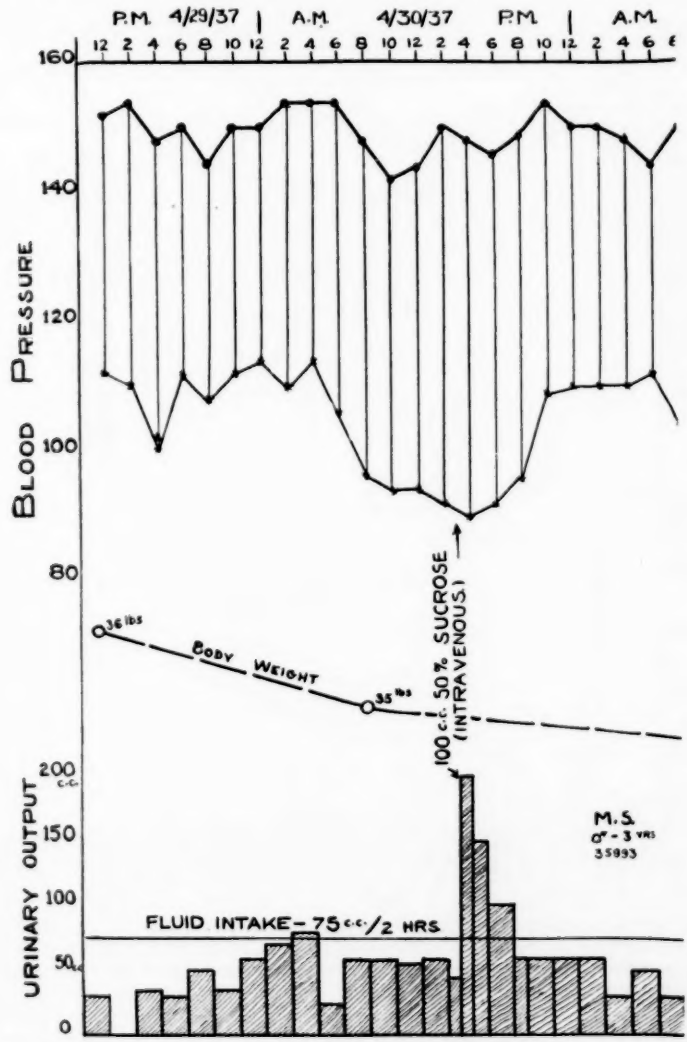

FIG. 3.—Failure of intravenous injection of hypertonic sucrose (50%) to lower the elevated blood pressure, while producing free diuresis.

Figure 5 is the chart of another patient with hypertension and hypertensive encephalopathy, whose period of observation began at 4 P.M., May 29, 1939. After the patient had been observed for

a period of 20 hours, during which time his urinary output, fluid intake, and blood pressure were carefully noted, he had a convulsion at 1 P.M., May 30, 1939, which was associated with a sharp rise in the diastolic blood pressure (this elevated diastolic reading was obtained while the patient was still convulsing). As the patient began to relax from the convulsion (the diastolic pressure had

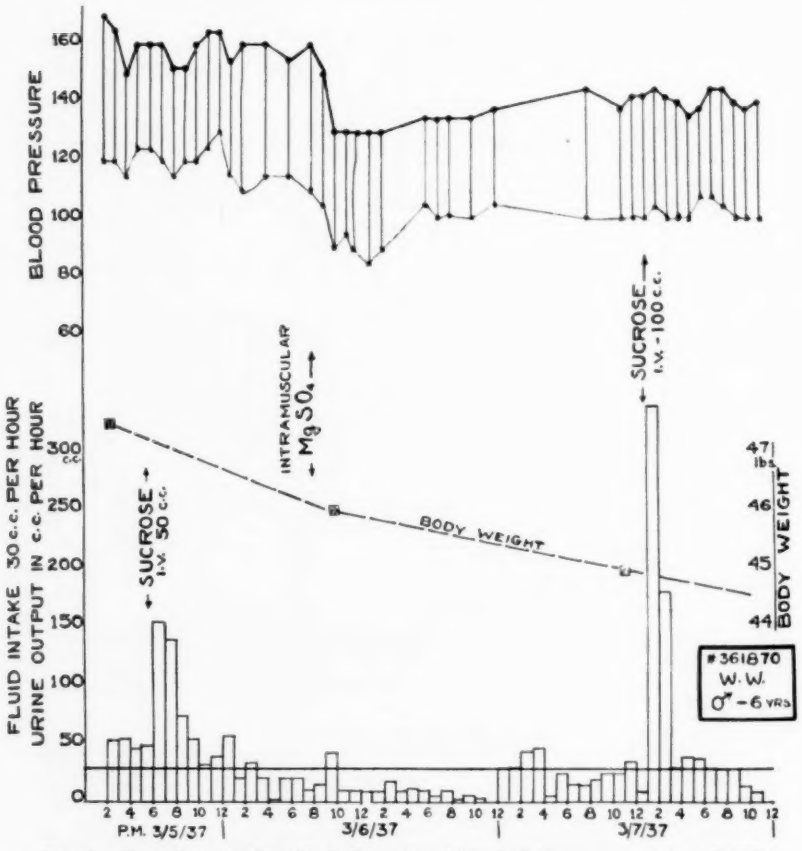

FIG. 4.—Free diuresis (dehydration) produced by the intravenously injected 50% sucrose—without any reduction of the blood pressure, followed by a reduction of the blood pressure produced by the intramuscular injection of $MgSO_4$—without accompanying diuresis.

already begun to fall), 75 cc. of 50% sucrose were given intravenously. A marked increase in urinary volume followed, with no significant alteration in the blood pressure. At 5 P.M., 2 hours after the sucrose diuresis had subsided, the patient had another convulsion. Following this second convulsion, magnesium sulphate was injected and was followed by a rapid fall in the blood pressure,

both systolic and diastolic, without any increased urinary output. Concomitant with the fall in blood pressure, the patient became alert and interested in his surroundings. It is pertinent to note that the blood pressure both during and after the second convulsion was at the same high level recorded prior to the first convulsion, and only after the magnesium sulphate injection was there any significant depression of the hypertension. Occasionally, immediately

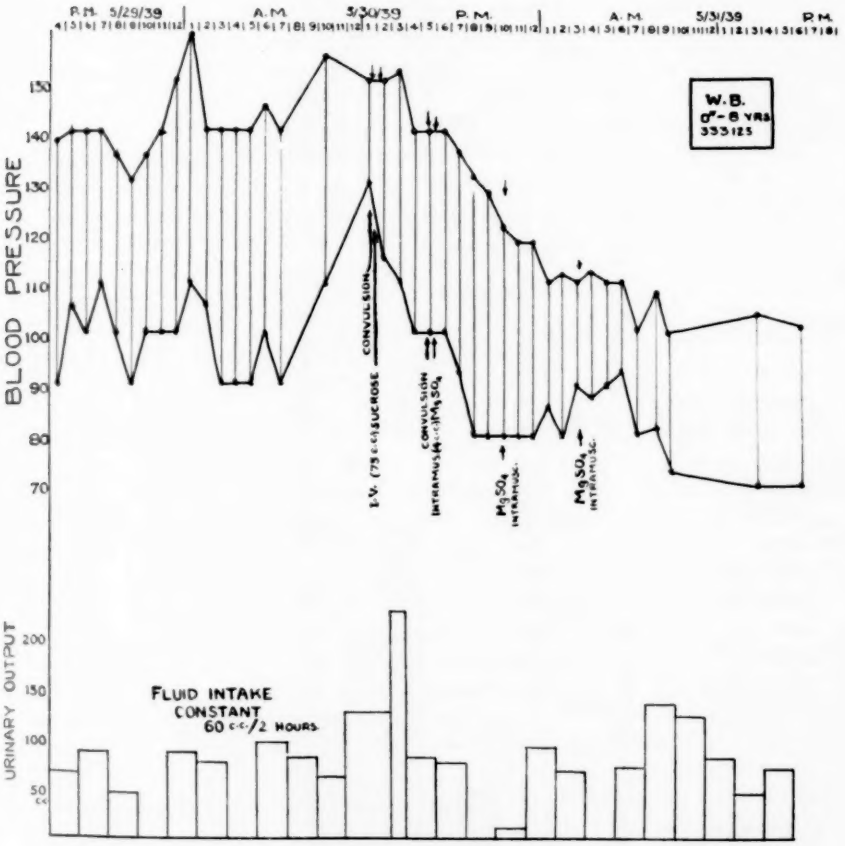

FIG. 5.—Reduction of the blood pressure by $MgSO_4$ after 50% sucrose given intravenously had produced a free diuresis but had failed to reduce the elevated blood pressure.

after sucrose is given, there is a transient elevation in the blood pressure (Fig. 6). This we have attributed to a temporary increase in blood volume induced by the hypertonicity of the sucrose solution, drawing fluid into the blood stream. Such an increase of blood volume has been found following sucrose administration.[6] The giving of sucrose to acutely hypertensive glomerulonephritics

is not without danger for this reason. We have seen two instances where such patients were thrown into acute cardiac failure, presumably due to the sudden increase in blood volume.

The data thus far presented demonstrated that magnesium sulphate reduces the elevated blood pressure in these patients without producing diuresis. It is maintained, by those who hold that

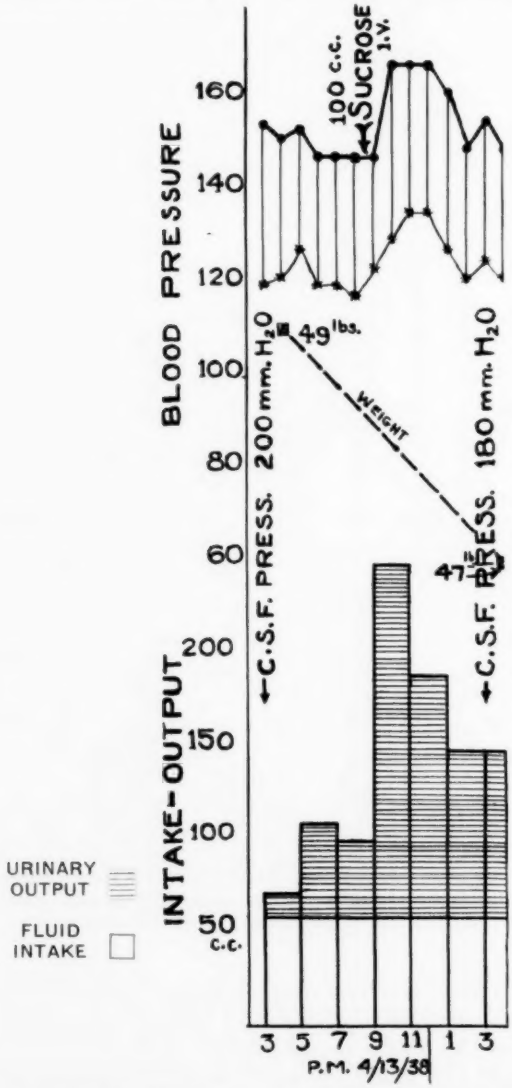

FIG. 6.—The relatively normal cerebrospinal fluid pressure in a child with hypertension and encephalopathy. Also the rise of the arterial blood pressure following the sucrose administration.

magnesium sulphate is operative through its dehydrating properties, that even though general dehydration might not occur with the small doses used, there does occur *localized cerebral dehydration*.[1] However, the inefficacy of hypertonic sucrose as a blood pressure reducing agent militates against this point of view. It has been amply demonstrated[5,9] that 50% sucrose produces a marked fall in intracranial pressure, obviously through cerebral dehydration. Still with doses of hypertonic sucrose large enough to produce loss of appreciable quantities of body water, and by inference cerebral dehydration, no fall of the elevated blood pressure occurred. Thus, even if following the administration of magnesium sulphate, local cerebral dehydration were to occur (in the absence of general dehydration), it would seem unreasonable to conclude that the fall in blood pressure elicited by the magnesium sulphate did result from this cerebral dehydration. Similar observations were made on a group of patients with malignant hypertension and hypertensive encephalopathy by Murphy *et al*,[10] who report that following the injection of intravenous sucrose there was a marked fall in intracranial pressure, with no fall in the blood pressure. In fact, in accord with our observations, these investigators noted a slight rise in blood pressure after the sucrose injection.

Since magnesium sulphate apparently does not act by dehydration either generalized or local, in effecting reduction of the acute hypertension of patients with acute glomerulonephritis, what then is the mechanism of its action?

It has been demonstrated by Pickering[11] and others[12] that the hypertension of acute glomerulonephritis is dependent upon spasm of the smaller arteries producing increased peripheral resistance. It is known that magnesium can relax smooth muscle, including that of the vascular wall. In previous experiments,[13] magnesium sulphate was effective in reducing the blood pressures of rats rendered hypertensive by large doses of ergotamine tartrate. Similarly, it produced relaxation of the smooth muscle of the guinea-pig uterus in Dale anaphylactic experiments. Hoff *et al*.[7] in animal experiments showed that magnesium sulphate produced lowering of blood pressure by its vasodilating action. It is extremely dubious whether the depressing action that magnesium sulphate is known to produce on the heart is responsible for the fall in blood pressure noted in these studies, for the blood concentrations of magnesium necessary to produce cardiac change[14] could not have been attained with doses of magnesium sulphate employed in this study. *Therefore, it might be concluded that magnesium sulphate lowers the blood pressure of the hypertensive child with acute glomerulonephritis by relaxing the existing generalized vasospasm through local action on the smooth muscle of the small blood-vessels.*

Blackfan[2] has inferred that this hypertension, which is dependent upon vasospasm, is induced in a large measure by cerebral edema,

since he observed increased cerebrospinal fluid pressure in his patients. However, he, too, seems uncertain as to whether the increased intracranial pressure is the primary event, since, according to him, none of the recorded pressures approach in any degree the magnitude of spinal fluid pressure necessary (800 mm. water) to produce the degree of hypertension noted in the glomerulonephritic. One of our cases (Fig. 6) showed the presence of hypertension in a child with very slightly elevated cerebrospinal fluid pressure.

Whether varying degrees of cerebral edema are present in all patients with acute glomerulonephritis having hypertension is not clear, nor is the mechanism of the occurrence of edema, when present, well understood. One possible explanation for this occurrence of edema may be some alteration in the cerebral circulation dependent upon vasospasm. Lewis and Gelfand[8] have shown that in the capillaries distal to constricted arterioles there is increased permeability, as evidenced by exudation of fluid and diapedesis of red blood cells. However, that this phenomenon does occur in the brains of these patients has not been proven.

It is extremely difficult in the clinical consideration of hypertension in the child with acute nephritis to disregard some mention of the acute hypertensive encephalopathic episodes. The sequence of events during such attacks would appear to be: 1, a sudden rise in the blood pressure; 2, cerebral symptoms, such as stupor, headache, convulsions; 3, a fall in the blood pressure; and finally, 4, disappearance of the cerebral symptoms. As to the etiology underlying the cerebral attack, the general opinions may be divided into two groups, one being that cerebral edema is the cause and the other, that cerebral anemia (anoxemia) is the basis for the attack. That magnesium sulphate relieves the attack is well recognized, and that the disappearance of the attack is preceded by a fall in the blood pressure is also well known. We have demonstrated that magnesium sulphate reduces the elevated blood pressure without producing dehydration, and further in Figure 5 we present a case where the encephalopathic attack was not relieved by dehydration with sucrose. These observations seem at least to cast some doubt on the theory that cerebral edema is the basis for the encephalopathic episode.

The edema of the brain that has been shown to exist in these patients might be considered as an added factor in the symptom-complex, exaggerating the cerebral symptoms but not its primary cause. The induction of dehydration very likely relieves that part of the symptomatology dependent on the cerebral edema.

While the evidence presented seems opposed to the "cerebral edema" hypothesis, it does not follow that it sustains the "cerebral anoxemia" theory. Nevertheless, the rapid disappearance of the cerebral symptoms following vasorelaxation with magnesium sulphate does apparently lend some slight weight in the direction of this latter possibility.

There are many instances where the recommended dose of magnesium sulphate (0.2 cc., 50% magnesium sulphate per kilo body weight repeated every 4 hours) fails to lower the elevated blood pressure in these acute nephritic patients. In each such instance, with the possible exception of 1 of our patients, there was a fairly large urinary output (600 to 1000 cc. daily). Although we have no

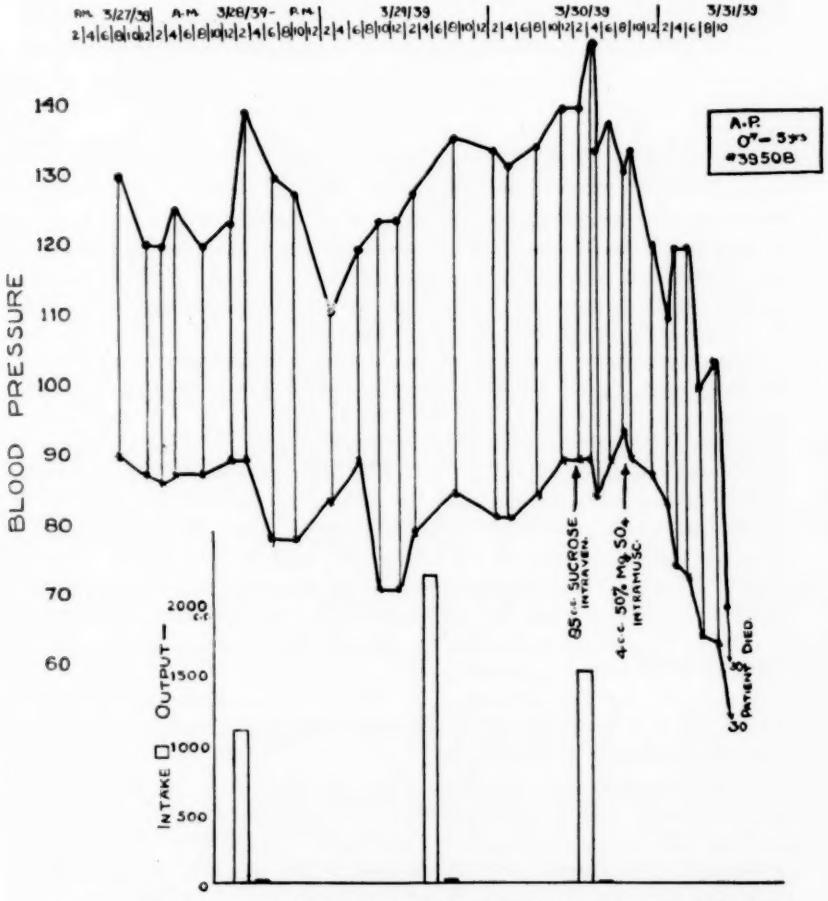

FIG. 7.—The exaggerated effect of $MgSO_4$ in lowering the blood pressure in an anuric patient.

data on the level of blood magnesium obtained in these patients, it seems probable that the failure in these instances of the magnesium sulphate to reduce the blood pressure may have been due to its rapid excretion from the body, with a failure to obtain a sufficiently high concentration of it in the body fluids for its physiologic action. Studies of Hoff, Smith and Winkler[7] would seem to

substantiate this, for they found that a definitely elevated level of blood magnesium (3 to 5 m.Eq.) had to be attained to produce a fall in blood pressure. They further demonstrated that there was some correlation between the level of blood magnesium and the amount of fall in blood pressure. These data suggest that patients with large urinary outputs require larger doses of magnesium sulphate than employed by us to obtain a reduction in blood pressure. Figure 7 is the blood pressure and fluid intake—output record of a 5-year-old boy with acute glomerulonephritis, who had anuria. The record extends over his complete hospital stay, although there was a history of anuria for 2 days prior to his hospitalization. On the fourth day of his anuria, when the blood pressure was rising, he was given 85 cc. of 50% sucrose intravenously. This was followed by a rise in the blood pressure but no diuresis. Six hours later he was given one intramuscular injection of a therapeutic dose of magnesium sulphate. This was followed by a precipitate decline in the blood pressure, during which the patient expired. (While magnesium sulphate may have adversely affected this patient, we feel that his death was primarily due to uremia.)

This case is presented because it is felt that it summarizes several of the points which we have already advanced. First, it shows conclusively, that magnesium sulphate is effective as a blood pressure reducing agent without producing dehydration. It is analogous to the experiments performed by Hoff *et al.*[7] where urinary excretion in their animals was suppressed by ligation of the ureters, prior to the administration of magnesium sulphate, so that the magnesium sulphate could be maintained at desired high levels in the body fluids. Thus the injection of one dose of magnesium sulphate into this anuric patient produced a maximal effect on the blood pressure. It further illustrates a possible danger of administering magnesium sulphate to an anuric patient.

Summary. In the patient with acute glomerulonephritis and hypertension: 1. Magnesium sulphate lowers the blood pressure without producing dehydration.

2. The intravenous administration of hypertonic sucrose produces diuresis, and generalized and cerebral dehydration, without lowering the blood pressure. Occasionally it elevates the blood pressure. The dangers of this secondary rise in blood pressure in the acute nephritic are pointed out.

3. Magnesium sulphate in the doses employed may be ineffectual in patients with large urinary volumes.

4. The mechanism by which magnesium sulphate reduces elevated blood pressure is discussed.

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ALIMENTARY AZOTEMIA: A CLINICAL SYNDROME OCCURRING AS A PART OF THE BLEEDING PEPTIC ULCER COMPLEX.

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The occurrence of increased blood urea values in cases of bleeding peptic ulcer was first observed by Sanguinetti[6] in 1934. Since that time the observation has been repeated by several writers and numerous theories have arisen as to the causation of the syndrome. Of the many theories, the three chief ones were dehydration and starvation (Meyler,[5] 1933; Alsted,[1] 1936); shock (Crohn,[3] 1939) and absorption of digested blood (Sanguinetti,[6] 1934; Christiansen,[2] 1935; Schiff, Stevens, *et al.*,[9] 1939; and Kaump and Parsons,[4a,b] 1940). Other writers likened the condition to so-called "hepatorenal syndrome."

The importance of the syndrome of increased blood urea in these cases has been repeatedly emphasized. Its value in prognosis has been shown by Schiff[8] in a report of 53 cases of hematemesis or melena in 1939. In a recent communication Schiff[7] reported 133 cases of hematemesis and melena. The blood urea nitrogen exceeded 30 mg. per 100 cc. in 78 of the cases and was 50 mg. per 100 cc. or more in 26 of the 78 cases. Of the patients with a blood urea nitrogen of 30 mg. per 100 cc. or more, 16.9% died; 34.6% of those with an elevation of 50 mg. per 100 cc. or more died and 63.6% of those with an elevation of 70 mg. per 100 cc. or more died. In the 57 patients with a blood urea nitrogen of less than 30 mg. per 100 cc. there were no deaths, excluding 2 cases of ruptured aortic aneurysm.

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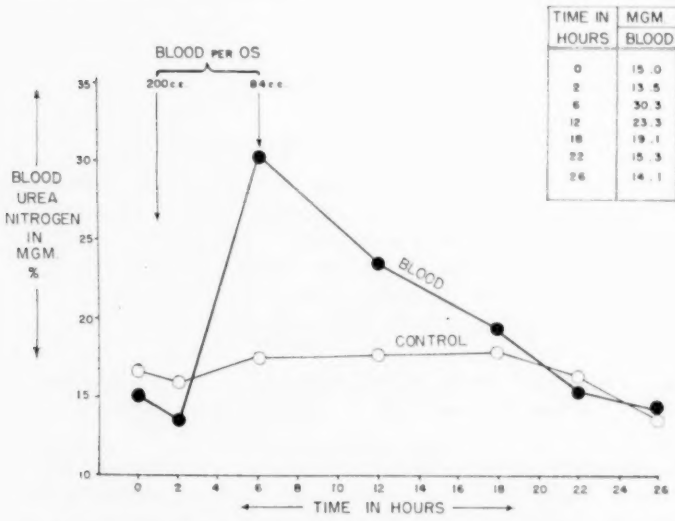
In the treatment of bleeding peptic ulcer the condition is also of importance. In a case where one is in doubt as to whether or not to operate, an increased blood urea due to renal or hepatic involvement might influence the decision far more than an elevation due to absorption of digested blood. It was because of this manifest difference in the importance of the syndrome depending on its cause that we started the present studies.

Causation of the Increased Blood Urea Values. In 13 experiments, on healthy dogs, whole beef blood was administered by stomach tube in large single and divided doses. A maximum blood urea nitrogen concentration was attained in all cases in from 5½ to 19 hours, depending on the amounts of blood given and the number of doses. The return of blood urea nitrogen to normal levels occurred in from 6 to 17½ hours following the last administration of blood as shown in Chart I.



TIME IN HOURS	MGM % B.U.N.	
	BLOOD	CONTROL
0	15.0	16.5
2	13.5	15.8
6	30.3	17.2
12	23.3	17.5
18	19.1	17.7
22	15.3	16.3
26	14.1	13.5

Chart I.—The effect of blood in the production of alimentary azotemia. The solid circles represent the blood urea nitrogen curve of the dog given blood by stomach tube while the hollow circles represent the curve of the control animal.

In a second series of ten experiments, 5 dogs were given beef blood cells by stomach tube in divided doses, and 5 dogs were given beef plasma in divided doses.

The 5 dogs given blood cells showed an elevation of blood urea nitrogen above normal within 4 hours and a maximum concentration at intervals between 5 and 12 hours. The return to normal levels required from 12 to 17 hours following the last dose of blood cells.

The 5 dogs given beef plasma by stomach tube showed a longer interval between first administration of plasma and the initial rise of

blood urea nitrogen, occurring from 4 to 11 hours. The maximum concentration was apparent at intervals of from 8 to 11 hours, 1 dog showed no elevation above normal. The return of the blood urea nitrogen to normal following the last dose of plasma required from $5\frac{1}{2}$ to 20 hours. It is evident from Chart II that the blood urea nitrogen values were higher for the animals that received blood cells than for the animals that received plasma. This difference occurred even when the doses of plasma were double that of cells.

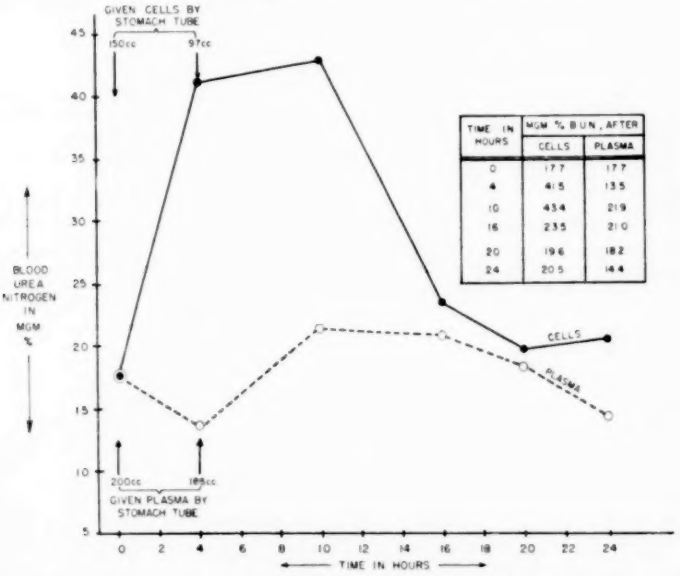


CHART II.—The comparative effects of blood cells and blood plasma in the production of alimentary azotemia. The solid line represents the blood urea nitrogen curve of the dog given red blood cells by stomach tube while the broken line represents the curve on the animal given blood plasma in the same manner.

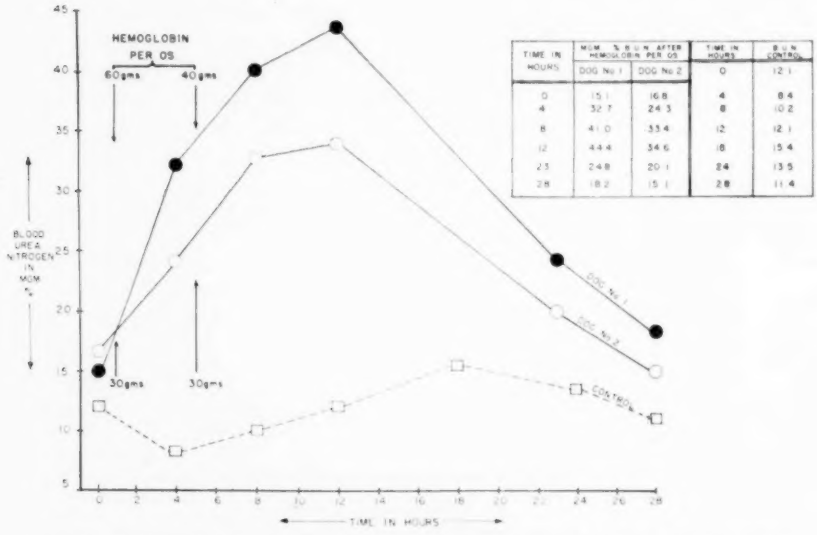
To carry this aspect of the investigation further, another experiment was done using 2 dogs. One dog was given 60 gm. of pure hemoglobin in two 30-gm. doses 4 hours apart. The second dog received 100 gm. of pure hemoglobin in one 60-gm. and one 40-gm. dose 4 hours apart. As is seen in Chart III, both dogs showed an initial increase in blood urea nitrogen in 4 hours, a maximum concentration in 12 hours, and a return to normal in 28 hours. However, the dog that received the larger dose of hemoglobin showed consistently higher blood urea nitrogen values.

Blood urea nitrogen concentration determinations were made on 2 cross-circulated dogs in terminal traumatic shock of 3 hours' duration. These values were 21.9 mg. per 100 cc. and 22.9 mg. per 100 cc. respectively. These were only slightly elevated above normal, and represent what is in many cases only the upper limit of

normal. Autopsy of both dogs revealed gross hemorrhagic congestion of the mucosa of the entire small bowel.

Chart I, of the blood urea nitrogen curve following administration of whole blood in the dog, agrees with Schiff *et al.*[9] similar experiments on humans.

"Alimentary Azotemia": A Proposed New Term. The name azotemia has been applied to this syndrome ever since Sanguinetti[6] wrote his first description of it. The word azotemia means the presence of urea or other nitrogenous bodies in the blood especially in increased amounts.



TIME IN HOURS	MGM. % B.U.N. AFTER HEMOGLOBIN PER OS		TIME IN HOURS	B.U.N. CONTROL
	DOG No. 1	DOG No. 2		
0	15.1	16.8	0	12.1
4	32.7	24.3	4	8.4
8	41.0	33.4	8	10.2
12	44.4	34.6	12	12.1
23	24.8	20.1	18	15.4
28	18.2	15.1	24	13.5
			28	11.4

Chart III.—The effect of hemoglobin in the production of alimentary azotemia. The two solid lines represent the blood urea nitrogen curves of dogs given hemoglobin by stomach tube and the broken line represents the curve of the control animal.

Reasoning from analogy to the commonly used term "alimentary glycosuria" (which might be more properly termed "alimentary hyperglycemia") it seemed logical to us that the urea syndrome be termed "alimentary azotemia." The mechanism in each case is the same and the adjective is used in both instances to differentiate the condition under consideration from a similar one in result but a different one in causation. Use of the designation "extrarenal azotemia" is not definitive enough and furthermore leads to confusion with the so-called hepatorenal syndrome which we believe is not at all related to the condition we are considering.

Conclusions. Alimentary azotemia occurs in cases of massive hemorrhage into the intestinal tract. This in turn most often results from a bleeding peptic ulcer. The degree of the azotemia is of considerable prognostic significance, high blood urea nitrogen

values being associated with high mortality. This is probably because the increase in blood urea nitrogen is a measure of the amount of blood lost. Our experiments indicate that the increase is due to absorption of digested blood, and therefore for this condition the name "alimentary azotemia" is proposed. Finally, we have shown that the increase is mainly due to the erythrocyte fraction of blood (and in particular to its contained hemoglobin), while the plasma fraction plays a distinctly secondary rôle.

Alimentary azotemia, therefore, can be defined as an azotemia due to absorption of digested hemoglobin from the alimentary tract, the condition occurring clinically most often in patients with bleeding peptic ulcer.

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VITAMIN C STUDIES IN THE AGED.

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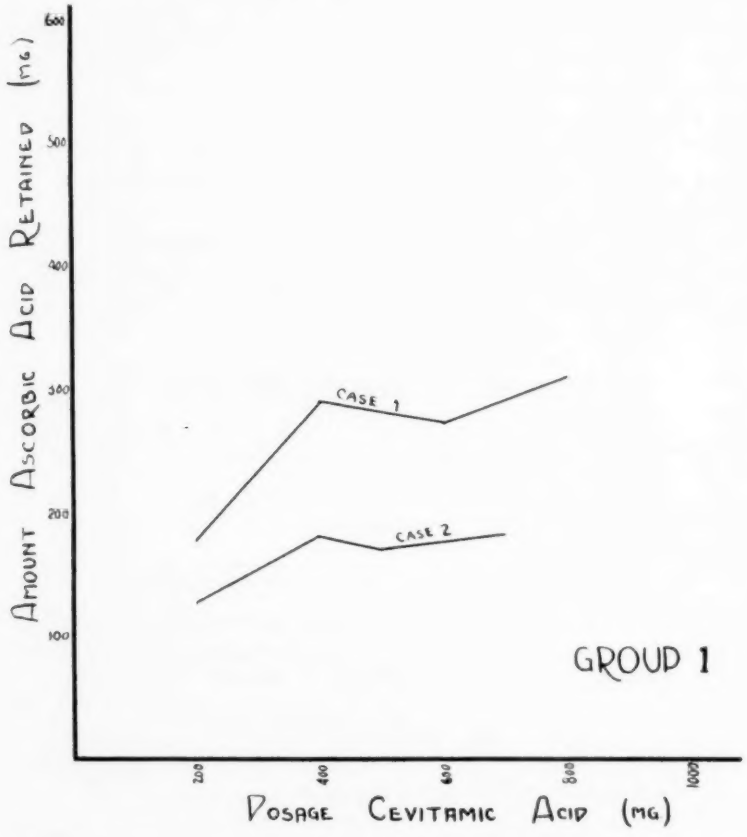
Vitamin C studies have been carried on extensively in infants and children and numerous articles have been written on the clinical significance of vitamin C deficiency in adults. Scant attention, however, has been paid to vitamin C studies in the aged. The only reports thus far have been those of Gander and Niederberger[1] and Kirchmann.[3] Gander and Niederberger administered cevitamic acid to a series of 14 patients (average age, 73 years) in daily doses of 200 mg. for a period of 4 days, followed by daily doses of 400 mg. In most of their cases urinary excretion of cevitamic acid did not increase until a total of 2000 mg. had been received. Kirchmann determined the cevitamic acid levels in a series of 50 patients, ranging in age from 50 to 87 years. Only 1 patient who had been living on an exclusively vegetarian diet for years was found to have the so-called normal cevitamic acid level of 1 mg. per 100 cc. No American investigators, to the best of our knowledge, have reported on vitamin C studies in the aged. It was therefore thought of interest to investigate vitamin C retention and excretion in aged individuals.

This study is based on a series of 25 so-called "normal" aged men and women. Their ages ranged from 66 to 83 years; 14 were men and 11 were women. The subjects who were chosen for this study were individuals who were not suffering from any active disease, were housed in the "Home" division of the institution and were ambulatory. In 10 of the cases, oranges, tomatoes and lemons were part of their dietetic intake.



Method. The amount of cevitamic acid* in the blood 1 hour after the noon-day meal and in the urine at the end of 24 hours was determined. These readings were regarded as our controls. Then, varying amounts of cevitamic acid were administered by mouth, starting with a dosage of 100 mg. and increasing this by 100 to 200 mg. doses over a period of time. The cevitamic acid was gradually increased until the saturation point was reached as evidenced by a sharp drop in the curves showing the amount of cevitamic acid retained. This was computed by subtracting the number of milligrams excreted from the amount given, as plotted against the

* The cevitamic acid, oral and injectable, was supplied through the courtesy of Hoffmann-La Roche, Inc., Nutley, N. J.

TABLE 1.

Case No.	Age.	Sex.	Date.	Dose of cevitamic acid (mg.).	Cevitamic acid in blood (mg. per 100 cc.).	Urinary excretion of cevitamic acid (mg. per diem).	Cevitamic acid retention (mg.).
1	76	♂	4- 5-40	Control	0.2	9	
			4-17-40	200	1.1	21	179
			4-26-40	400	2.4	110	290
			5- 5-40	600	2.8	327	273
			5-17-40	800	3.1	490	310
2	79	♂	4-11-40	Control	1.7	82	
			4-26-40	200	2.9	73	127
			5- 4-40	400	3.1	219	181
			5- 9-40	500	Not determined	329	171
			5-18-40	700	3.8	517	183
3	77	♀	7- 9-39	Control	0.4	10.8	
			7-15-39	100	0.4	18.8	81
			7-23-39	200	1.0	14.3	186
			8-27-39	400	0.92	97	303
			9-19-39	600	Not determined	143	257
			10-27-39	700	Not determined	340	360
4	77	♂	4-10-40	Control	0.8	38.8	
			4-16-40	200	1.4	59.8	140
			4-25-40	400	2.1	179	221
			5- 5-40	600	3.1	312	288
			5-12-40	800	3.8	490	310
5	72	♀	5- 1-40	Control	0.6	11.8	
			5- 8-40	200	1.3	29.9	170
			5-16-40	400	2.9	210	190
			5-24-40	500	3.2	380	120
			6- 2-40	700	3.6	430	270
6	72	♂	5- 5-40	Control	0.6	7	
			5-16-40	200	1.0	26	174
			5-24-40	400	2.1	89	311
			6- 1-40	600	0.9	133	467
			6-17-40	900	3.2	390	510
7	73	♀	5- 6-40	Control	0.3	7.2	
			5-12-40	200	0.6	19	181
			5-18-40	400	1.1	67	333
			5-26-40	600	1.8	104	496
			6- 2-40	800	3.6	214	586
			6-10-40	1000	3.8	397	603
8	69	♀	5- 6-40	Control	0.7	11	
			5-12-40	200	1.8	30	170
			5-18-40	400	2.4	103	297
			5-25-40	600	Not determined	194	406
			6- 2-40	800	Not determined	340	460
9	73	♀	8-27-39	Control	0.42	22	
			9-21-39	200	0.78	19	181
			10-18-39	400	1.2	77	323
			11- 4-39	500	Not determined	90	410
			11-29-39	600	1.9	122	478
			12-25-39	800	2.7	480	320
			1-14-40	1000	3.1	540	460
10	79	♂	3-29-40	Control	0.7	17.9	
			4- 6-40	200	Not determined	86.8	112
			4-17-40	300	1.9	129	171
			4-28-40	500	2.9	380	110
			5- 3-40	700	Not determined	410	290
			5-12-40	900	Not determined	650	250

TABLE 1—*Continued.*

Case No.	Age.	Sex.	Date.	Dose of cevitamic acid (mg.).	Cevitamic acid in blood (mg. per 100 cc.).	Urinary excretion of cevitamic acid (mg. per diem).	Cevitamic acid retention (mg.).
11	73	♂	7-17-39	Control	1.7	22.6	
			8-24-39	200	1.6	67	133
			9-14-39	400	1.4	107	293
			10- 7-39	500	1.6	129	371
			11-10-39	600	1.9	390	210
			11-27-39	700	2.4	520	180
12	73	♂	7-14-39	Control	0.4	23	
			9-21-39	200	1.0	11	189
			10- 7-39	400	Not determined	97	303
			11-10-39	500	2.3	390	110
13	66	♀	7- 5-39	Control	0.9	0	
			7-16-39	100	1.0	7	93
			7-23-39	200	1.2	13	167
			7-30-39	300	1.6	82	218
			8-22-39	400	1.4	17	383
			8-30-39	500	1.0	17	483
			9-14-39	600	1.1	38	562
			10-20-39	800	2.1	173	627
			11-27-39	1000	2.7	830	170
14	68	♀	1- 2-40	Control	0.38	11.3	
			1-27-40	200	1.7	29	171
			2-29-40	400	2.7	53	347
			3-16-40	500	2.8	99	401
			3-29-40	700	2.6	177	523
			4-10-40	900	3.7	410	490
15	66	♀	5- 1-40	Control	0.73	16	
			5- 9-40	200	1.3	39	161
			5-20-40	400	1.9	98	302
			6- 2-40	600	2.6	167	443
			6- 7-40	800	3.4	314	486
			6-12-40	1000	Not determined	611	389
16	73	♀	4-25-40	Control	0.57	12	
			5- 5-40	200	1.0	34	176
			5-18-40	400	1.4	81	329
			6- 2-40	600	Not determined	136	464
			6- 7-40	800	2.9	380	420
			6-16-40	1000	3.8	642	358
17	80	♂	7-14-39	Control	1.2	13	
			7-25-39	100	0.8	30	70
			9- 3-39	200	1.3	33.5	164
			9-30-39	400	1.8	58	342
			10-17-39	600	2.0	110	490
			11-24-39	800	2.3	290	510
			12- 7-39	900	2.6	580	320
18	81	♂	11-19-39	Control	0.5	10.1	
			12-19-39	200	1.9	29.7	170
			1- 7-40	300	2.8	40.2	260
			2-19-40	500	2.6	106	394
			3- 3-40	600	3.5	212	388
			3-11-40	800	3.9	479	321
19	71	♀	8-15-39	Control	0.92	4.1	
			9-19-39	200	0.9	41	159
			10-16-39	400	1.3	120	280
			11-29-39	500	1.5	122	378
			12- 5-39	700	2.6	350	350

TABLE 1—*Continued.*

Case No.	Age.	Sex.	Date.	Dose of cevitamic acid (mg.).	Cevitamic acid in blood (mg. per 100 cc.)	Urinary excretion of cevitamic acid (mg. per diem).	Cevitamic acid retention (mg.).
20	68	♂	4- 4-40	Control	0.74	32	
			4-10-40	200	1.4	32	168
			4-17-40	300	1.8	97	203
			4-21-40	500	2.8	126	374
			4-29-40	700	3.3	410	290
			5- 7-40	900	Not determined	698	202
21	68	♀	7-23-39	Control	1.6	76	
			8-24-39	100	1.4	84	16
			8-31-39	300	1.8	116	184
			9-14-39	500	3.1	219	281
			9-24-39	700	Not determined	419	281
			10-17-39	900	3.9	710	190
22	83	♂	8-17-39	Control	0.6	12.2	
			8-30-39	200	1.4	19.9	180
			9-11-39	400	2.0	37	363
			9-30-39	500	2.7	113	387
			10-31-39	600	1.9	260	340
			11-19-39	800	3.1	620	180
23	61	♂	4- 1-40	Control	0.39	14.8	
			4- 9-40	200	0.9	34	166
			4-18-40	400	1.4	126	274
			4-29-40	600	2.9	239	361
			5- 5-40	800	3.3	608	192
24	79	♂	7- 3-39	Control	0.7	13.6	
			7-16-39	100	1.5	22.3	78
			9-14-39	200	1.3	19.8	180
			9-29-39	400	Not determined	77	323
			10- 9-39	600	0.95	190	410
			10-30-39	800	2.2	610	190
25	81	♂	5- 3-40	Control	0.4	2	
			5- 9-40	200	2.4	19.7	180
			5-16-40	400	2.3	97	303
			6-24-40	600	3.3	219	381
			6- 2-40	800	3.8	288	512
			6-16-40	1000	3.6	496	504

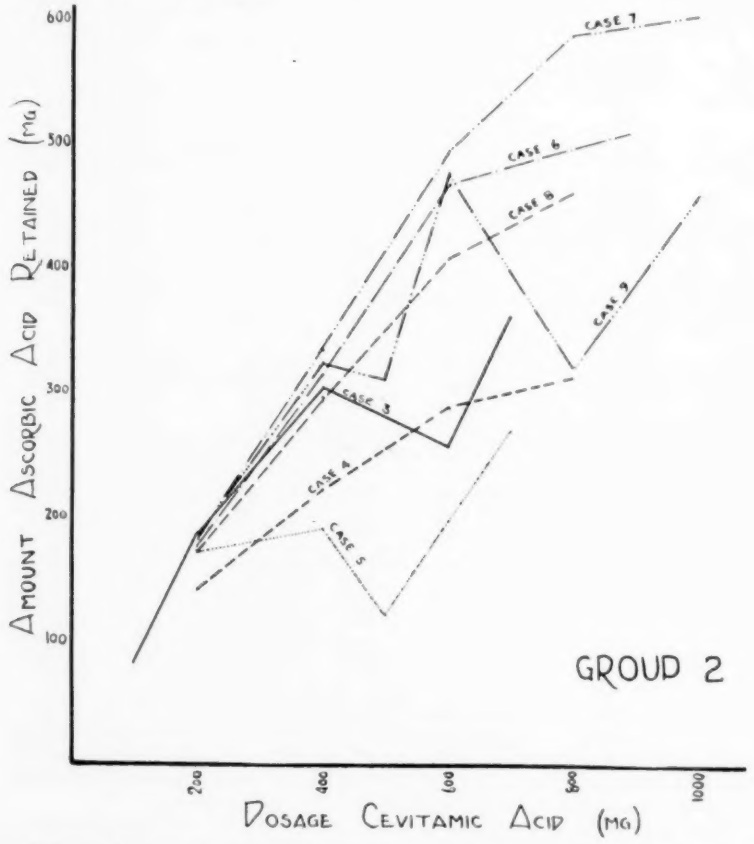
amount of cevitamic acid administered. No more than 1000 mg. of cevitamic acid were given as a single dose to any one subject because diarrhea was experienced by some with this dose. The periods chosen for the administration and determination of vitamin C were selected far enough apart to ensure the complete excretion of the previous dose.

The blood levels of cevitamic acid were determined by Tillmans' method as described by Pijoan and Klemperer[4] and the determination of cevitamic acid in the urine was made by a modification of Tillmans' method as employed by Harris and Ray.[2]

Clinical Studies. The dosage of cevitamic acid, the days on which it was given, the blood levels, the urinary excretion and the amount retained in the system are given in Table 1. In the accompanying graphs the number of milligrams of cevitamic acid which was retained has been plotted against the number of milligrams of cevitamic acid administered.

The levels of the retained cevitamic acid seemed to indicate three types of curves:

1. A more or less constant level (Cases 1 and 2).
2. A constant upward trend during the period these experiments were carried out (Cases 3 to 9).
3. A rise until a peak was reached and from there on a downward trend (Cases 10 to 25).

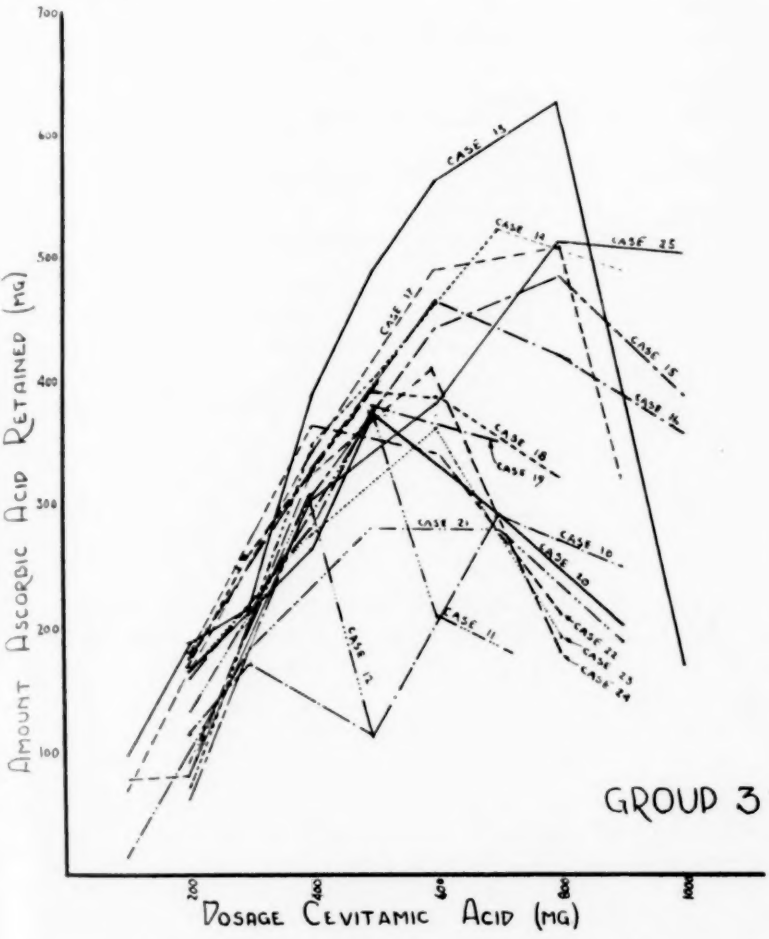


When the cevitamic acid was given in large amounts, the blood levels of cevitamic acid were likewise found to be appreciably high. The maximum levels were reached at the end of $\frac{1}{2}$ to 1 hour, whether administration was oral or intravenous. The highest level reached in the blood after 1000 mg. of cevitamic acid given by mouth was 3.8 mg. at the end of 1 hour and when given intravenously the maximum level varied in 1 case from 4.5 mg. in 1 hour with a dose of 400 mg. to 4.2 mg. in $\frac{1}{2}$ hour in another case with a dose of 1000 mg.

Comment. When cevitamic acid was given in comparatively large amounts to 25 so-called "normal" aged individuals, cevitamic acid retention was noted in most of the subjects and the blood

levels of cevitamic acid were likewise appreciably high. The cevitamic acid retention curves were grouped as follows:

GROUP 1. In this group a more or less steady level of retained cevitamic acid was noted. Irrespective of the amounts given, the excretion and retention closely followed the same pattern. These levels would seem to indicate that the saturation point was reached with relatively smaller doses as compared with most of the subjects under study.



GROUP 2. In this group, the cevitamic acid retention continued to increase notwithstanding the fact that constantly larger doses were administered. No saturation point was observed during the time these experiments were carried out. It would be logical to assume from these curves that the subjects in this group required increasingly larger doses of cevitamic acid.

GROUP 3. In this group comparatively large amounts of cevitamic acid seemed to be required before the levels of cevitamic acid retention showed a drop. It is difficult to explain just why there should be less retention with maximum doses of cevitamic acid, unless a reserve of sufficient magnitude had been stored in the system from the previous doses that further cevitamic acid was not required. In this group, the cevitamic acid retention level, after reaching the peak, showed a variable drop from a slight to a sharp descent.

The maximum blood levels of cevitamic acid did not show any appreciable changes which could be related to the avenue of administration, whether oral or intravenous. This was of special interest in view of the rôle which the factors of assimilation, absorption and utilization play in vitamin studies.

The relationship of cevitamic acid retention to arteriosclerosis, which more or less accompanies old age, was of interest to us. This phase of the study is still under investigation and no definite conclusions have been found.

Conclusions. In a series of 25 so-called normal aged individuals, who received comparatively large doses of cevitamic acid, only 2 showed a more or less constant saturation point. In the rest, high retention values were observed; in fact, in 7 cases the amount of retained cevitamic acid continued to increase throughout the experiment.

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SCARLATINIFORM ERYTHEMA WITH SYSTEMIC REACTION FOLLOWING INUNCTION WITH MERCURIAL OINTMENT.

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DURING the past 4 years (1936 through 1939), 8 patients were referred to this hospital with a diagnosis of scarlet fever in whom we believe mercurial ointment inunctions were responsible for the scarlatiniform erythema. This error is understandable when one remembers that such patients often have fever and other evidences of systemic infection. All of the patients gave the same history, namely, repeated inunctions with blue ointment for the treatment of pediculosis. Detailed description of the cases will be presented after a preliminary historical review.

It has long been known that mercury, however taken into the body, is capable of producing mild to severe systemic reaction

including scarlatiniform erythema. Indeed, Bonetus[6] in 1687 describes a case of "antipathy to mercury" in which the sensitive subject's hands and arms became red, itchy, and swollen merely on touching the metal. Other authors, Bell[5] in 1793, and Spens[13] in 1805, published reports concerning an erythema produced by mercurial inunction, but it was Alley[2] in 1810 who first gave an excellent description of the skin reaction and mentioned its close resemblance to the rash of scarlet fever. Alley classified the reactions as follows: *A*, hydrargyria mitis—without fever; *B*, hydrargyria simplex—with fever; *C*, hydrargyria maligna. He then described the above clinical types in some detail: "In *A*, there occurs an eruption of true miliary vesicles. The appearance of the vesicles is announced by a sense of heat and smarting on the surface of the skin. The only constitutional reaction is headache and nausea. The efflorescence, though not close at first, is gradually diffused over the whole surface of the parts affected so that they, and sometimes the entire body, present one uniform suffusion of tint. The color of the eruption recedes when pressure is applied and suddenly returns when pressure is removed. There may or may not be desquamation in this mild form. In *B*, the eruption is preceded by languor, restlessness and rigors, is accompanied by much itching and heat of the skin and the latter is considerably rough to the touch. There is also headache, whiteness of tongue and costiveness. The eruption may resemble rubella at this time. There is always greater or less fever (102°–106° F.) and the disease now also resembles measles. When on the decline, the eruption bears a great similarity to scarlatina anginosa. The cuticle separates here in larger areas than in the former, and desquamation is usually preceded by soreness of the throat. In *C*, there is a painful sense of burning on the skin surface. Soreness of the throat is prominent. The color of the eruption is darker, almost purple at times. Vesicles of large size are formed and there is edema of the subcutaneous tissue. Desquamation occurs in large flakes. The finger and toe nails may separate."

There have been many theories regarding the pathologic physiology of mercurial erythema. One of the most promising was proffered in 1888 by Lesser[10] who suggested that the mercury circulating in the blood stream caused paralysis of the sympathetic nerves with consequent capillary dilatation. That capillary dilatation is the primary effect of mercury on the skin is supported by the histologic studies of Almkvist[4] in 1922. In these studies he found that there was first vascular dilatation and transudation of fluid from vessels to tissue spaces, then cellular infiltration, and finally, bacterial invasion. He noted that the maximum capillary dilatation occurred at the summits of the papillæ, a fact which accounts for the punctate appearance of mercurial rashes and their close resemblance to the punctate erythema of scarlet fever.

Later literature is replete with reports of scarlatiniform erythema due to mercury in various forms and administered by various routes. Outstanding among these are papers by Alexander,[1] Caspary,[8] Allgeyer,[3] Thibierge,[14] Milian[11a] and Wright.[15]

Case Reports. Case 1.—(Hosp. No. 421.) S. K., a 22-year-old white male was admitted on Feb. 5, 1936, with a chief complaint of fever and rash of 2 days' duration. The patient had been applying an unspecified amount of blue ointment to the skin of the pubic region for 5 days prior to entry. On the fifth day of treatment he suddenly developed a temperature of 102.4° F. and felt chilly. On the sixth day there was a bright red generalized rash and on the seventh day of treatment he was referred to the hospital with a diagnosis of scarlet fever. Admission examination revealed a well-developed and well-nourished male who did not appear acutely ill. He complained of considerable itching of the skin. The temperature was 102.4°, the pulse 98, and the respirations 18. Examination of the skin revealed a bright erythema over the chest, abdomen, and extremities. The rash on the trunk was confluent and punctate in character, while on the extremities it was macular. The most intense erythema appeared in the pubic region, the site of application of the ointment. The face alone was clear.

Head: eyes, ears, nose negative. Mouth: teeth and gums normal. Tongue white. Palate normal. Pharynx: moderately red. Tonsils injected. *Neck:* no enlargement of lymph nodes. *Chest:* lungs clear; heart negative. *Abdomen:* negative. *Genitalia:* normal except for intense erythema over pubic region; no pediculi seen. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative.

Course in Hospital. On symptomatic treatment, the temperature fell to normal on the fourth day and remained so throughout the remainder of the hospital stay. On the fifth day the rash faded except for a small area over the pubic region. He was discharged from the hospital on the seventh day of his illness. There was no desquamation except at the pubic region.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

Case 2.—(Hosp. No. 537.) S. B., a 20-year-old white male, was admitted on Feb. 12, 1936. The patient had applied blue ointment for the treatment of pediculosis for 7 days prior to the onset of the present illness. He had used the ointment over his entire body with the exception of his face. On the seventh day of treatment he had malaise with fever of 102°. On the eighth day, his throat felt sore, and on the tenth day he developed a rash and was referred to this hospital with a diagnosis of scarlet fever. On entry, examination was as follows: Temperature 101.6°, pulse 100, respirations 20. The patient appeared acutely ill, with a livid eruption of fine punctate, closely-set papules over the trunk and extremities. The erythema was sharply demarcated at the neck and at the wrists and ankles. The face was clear.

Head: eyes, ears, nose negative. Mouth: profuse salivation; teeth normal; gums boggy and red. Pharynx: injected; tonsils small, injected. *Neck:* cherry-sized lymph nodes palpable. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* skin of pubic region showed fine desquamation as well as intense erythema. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative to routine examination, but Reinsch test for mercury was positive. Blood count: hemoglobin 85%. Red cells 3,700,000. White

cells 6200; neutrophils 82%, lymphocytes 9%, monocytes 9%. Throat culture: negative for *beta*-hemolytic streptococci.

Course in Hospital. The patient was given 10% sodium thiosulphate intravenously for 3 days. The temperature remained elevated at 101° and the rash persisted. On the sixth day of illness the patient was transferred to another hospital. At this time there was fine desquamation over the trunk; this was most evident in the axillæ and in the pubic region.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever. Mercury poisoning.

CASE 3.—(Hosp. No. 5062.) M. F., a 20-year-old white male, was admitted on Nov. 2, 1936. The patient had been treating himself for pediculosis for 10 days prior to entry. He had applied an unspecified amount of blue ointment to the groins, axillæ, and sternal region. On the tenth day of treatment there was sudden onset of headache, sore throat, and fever. On the next day he noticed a rash, first at the sites of application of the ointment, but soon becoming generalized. He was referred to this hospital with a diagnosis of scarlet fever. Examination revealed an acutely ill patient, with temperature 102.2°, pulse 110, and respirations 20. There was generalized erythema, punctate in the groins, axillæ, and over the sternum, but macular elsewhere. The eruption was most marked over the upper back where the lesions were hemorrhagic. The face was clear.

Head: eyes, ears, nose negative. Mouth: teeth—fair condition; gums soft and spongy; tongue beefy red. Pharynx: moderately red; tonsils injected. *Neck:* no lymph node enlargement. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* pubic hair shaved; there is excoriation of scrotal skin with dry scaling. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative; Reinsch test for mercury negative. Blood count: hemoglobin 90%. Red cells 4,000,000. White cells, 5800; neutrophils 83%, lymphocytes 12%, monocytes 4%, eosinophils 1%. Throat culture: negative for *beta*-hemolytic streptococci; positive for Vincent's organisms.

Course in Hospital. On symptomatic treatment, the temperature came to normal on the fifth day of illness; the rash faded and was completely gone on the seventh day after onset. Desquamation was present in the axillæ, groins, and sternal region.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 4.—(Hosp. No. 4964.) G. M., a 23-year-old white male, was admitted on Oct. 23, 1937. The patient had been using blue ointment in both groins for pubic pediculi for 2 days prior to onset at which time he noticed a bright, generalized erythematous rash. There were no other symptoms, but on the appearance of the rash he was referred to this hospital with a diagnosis of scarlet fever. On entry, the temperature was 98.8°, the pulse 80 and the respirations 20. He was not acutely ill. The skin presented a bright erythema, confluent over the trunk and blotchy over the extremities. The rash was purpuric in character over one small area on the anterior chest.

Head: eyes, ears, nose negative. Mouth: gums and teeth normal; tongue white. Pharynx: markedly reddened; tonsils large and red. *Neck:* small anterior cervical nodes palpable. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* normal. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative. Blood count: hemoglobin 80%. Red cells 5,040,000. White cells 6750; neutrophils 76%, lymphocytes 20%, monocytes 2%, eosinophils 2%. Throat culture: *Staph. aureus;* negative for *beta*-hemolytic streptococci.

Course in Hospital. At no time did the patient have fever. Daily urine examination was negative. He was discharged from the hospital on the sixth day of illness with the rash faded but not entirely clear. There was fine desquamation in the groins.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 5.—(Hosp. No. 5021.) J. L., a 31-year-old white male, was admitted on Aug. 19, 1938. The patient had been applying blue ointment to the entire body intermittently for the past month prior to entry. He was taken ill rather suddenly with high fever and a brilliant erythematous rash and was referred to the hospital with a diagnosis of scarlet fever. On entry he was acutely ill with temperature of 105°, pulse 120, respirations 22. The skin presented a bright confluent erythema over the trunk, becoming blotchy over the extremities. The face was clear.

Head: eyes, ears, nose negative. Mouth: teeth carious; gums reddened; tongue beefy red. Pharynx: red; tonsils out. *Neck:* no lymph node enlargement. *Chest:* lungs clear; heart: tachycardia, no enlargement, no murmurs. *Abdomen:* negative. *Genitalia:* pediculi present in pubic region. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative; Reinsch test for mercury negative. Blood count: hemoglobin 75%. Red cells 4,000,000. White cells 4200; neutrophils 52%, lymphocytes 47%, monocytes 1%. Throat culture: negative for *beta*-hemolytic streptococci.

Course in Hospital. The patient was given symptomatic treatment during which time the temperature ranged between 101° and 104° for the first 4 days, coming to normal on the fifth day. The rash faded with the subsidence of the temperature. A fine desquamation was noted over the trunk. The patient was discharged from the hospital on the eighth day of illness.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 6.—(Hosp. No. 6025.) C. P., a 21-year-old white male, was admitted on Dec. 11, 1938. He had used four tubes of blue ointment for the treatment of pediculosis. The ointment had been applied to the axillæ and groins for 1 week when he developed fever, sore throat, and an erythematous rash. He was referred to this hospital with a diagnosis of scarlet fever. On entry his temperature was 103°, pulse 120 and respirations 20. The skin examination revealed a generalized blush, lobster-red in color. There were vesicles superimposed on an intense erythematous base in the groin.

Head: eyes, ears, nose negative. Mouth: teeth in fair condition; gums spongy; tongue white. Pharynx: moderately red; tonsils out. *Neck:* no lymph node enlargement. *Chest:* lungs clear; heart normal except for tachycardia. *Abdomen:* negative. *Genitalia:* scaling erythematous eruption present; pediculi present in pubic region. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative. Blood count: hemoglobin 80%. Red cells 4,000,000. White cells 6200; neutrophils 84%, lymphocytes 14%, monocytes 2%. Throat culture: positive for Vincent's organisms. No *beta*-hemolytic streptococci grown.

Course in Hospital. With symptomatic treatment the temperature gradually fell to normal on the eighth day of the illness, but the rash had not completely faded until the tenth day. Desquamation appeared in the groins. This desquamation was fine or "branny" in character.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 7.—(Hosp. No. 1621.) E. K., a 17-year-old white male, was admitted on April 17, 1939. For 3 days prior to entry he had applied blue ointment because of pediculi. On the second day of treatment, he complained of soreness in his throat. The next day he had fever and a bright red rash and was referred to this hospital with a diagnosis of scarlet fever. On entry he appeared moderately ill. The temperature was 101°, pulse 100 and respirations 20. He was salivating quite profusely. The skin of the trunk was erythematous, and this erythema was most marked in the axillæ and groins where it was also punctate in character.

Head: eyes, ears, nose negative. Mouth: gums white and swollen. Pharynx: moderately injected; tonsils small, not remarkable. *Neck:* no enlarged nodes. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* erythema with vesiculation in pubic region and groins. Pediculi present. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine: trace of albumin present on admission; Reinsch test for mercury negative. Throat culture: *Strep. viridans;* no *beta*-hemolytic streptococci grown.

Course in Hospital. The patient's temperature remained elevated for 6 days, coming to normal on the seventh, at which time the erythema had also faded. There was some fine desquamation in the groins and axillæ; none elsewhere.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

CASE 8.—(Hosp. No. 2916.) J. H., an 18-year-old white male, was admitted on Aug. 10, 1939, with a 10-day history of intermittent applications of blue ointment to the skin of the axillæ and groins. On the tenth day of treatment he was suddenly seized with headache and fever of 102° to 103° F., followed in 24 hours by a generalized rash. His throat felt sore at the time of the appearance of the rash. He was brought to this hospital with a diagnosis of scarlet fever. Physical examination revealed a young adult who was quite ill, with a temperature of 102.2°, pulse 100, respirations 22. His skin presented a diffuse generalized erythema which was definitely purpuric in the axillæ and groins. In the latter areas there was also blistering.

Head: eyes, ears, nose normal. Mouth: gums normal; teeth in good condition; tongue white. Pharynx: injected; tonsils large, moderately injected. *Neck:* no enlarged nodes. *Chest:* lungs clear; heart normal. *Abdomen:* negative. *Genitalia:* purpuric erythema with blistering on both groins. *Extremities:* reflexes and joints normal.

Laboratory. Dick, Schultz-Charlton and Wassermann tests negative. Urine negative. Throat culture: *Staph. aureus;* negative for *beta*-hemolytic streptococci.

Course in Hospital. The temperature ranged from 101° to 103° for the first 4 days and then came to normal on the fifth day. The rash faded completely by the eighth day. There was considerable coarse desquamation in the axillæ and groins, but none elsewhere.

Discharge Diagnosis. Dermatitis venenata (mercury). No case of scarlet fever.

Comment. On reviewing the various clinical aspects of the foregoing 8 cases, it is seen that the blue ointment had been applied in the majority of cases from 5 to 7 days before a systemic reaction occurred and that the skin reaction was accompanied by fever of 101° or over in all but 1 patient (Case 4). The average duration of the rash was 7 days; Bossard[7] gives 5 days as the usual duration. In many areas the rash was described as a "punctate erythema"

but was further characterized as being a very bright red in color. Itching of the skin, described as a prominent symptom by some authors, was present in only 1 of these cases (Case 1). Desquamation followed in every case and was most pronounced at the site of application of the ointment. Milian[11b] states that the desquamation varies directly with the intensity of the eruption and ranges from a light branny flaking to a coarse exfoliation. He points out that it is not accentuated at the fingers and toes as in scarlet fever. It will be noted that 5 of the 8 patients at some time complained of sore throat, making the resemblance to scarlet fever all the more close. In none of the cases in which a blood count was reported was there a leukocytosis, the white counts ranging from 4000 to 7000. The eosinophilia mentioned by some authors was not present in this series. Mercurial stomatitis was present in only 2 of the 8 cases (25%), and this would appear to agree with the observations of Gaumond[9] and Milian[11b] who state that cutaneous manifestations of mercurial poisoning are usually not accompanied by mercurial stomatitis. Abnormal urinary findings (mercury in Case 2 and albumin in Case 7) were present only in those patients with mercurial stomatitis and were conspicuous by their absence in the remaining cases.

As regards diagnosis and, above all, the differentiation of these cases from scarlet fever, it would seem that the most helpful points are: 1, a history of recent exposure to mercurials, either by inunction or by injection; 2, the brilliancy of the erythema; 3, helpful laboratory data. The latter would include a negative Schultz-Charlton reaction, absence of leukocytosis, and absence of *beta*-hemolytic streptococci from the throat culture. The character of the rash and the character of the desquamation alone cannot be relied upon. Schamburg[12] has most aptly stated the problem: "It may be asserted that more errors of diagnosis both of commission and omission are made in connection with scarlet fever than with any other common eruptive fever. I am inclined to believe that the more frequent error is made in regarding as scarlet fever some affection accompanied by a scarlatinoid rash. Consciously or unconsciously we attribute more diagnostic weight to the existence of the rash than its importance warrants." And again, concerning desquamation, he says: "It cannot be too strongly expressed and impressed that all that scales is not scarlet. Scaling is the terminal stage of pathological changes in the skin which are by no means peculiar to scarlet fever."

Summary. Eight cases of scarlatiniform erythema with other evidences of systemic reaction are reported and described. Each of these reactions occurred following inunction with blue ointment (33% mercury) in the treatment of pediculosis. Because of the resultant fever and erythema, all of these patients were referred to this hospital with a diagnosis of scarlet fever. Despite the already

numerous reports of hydrargyria occurring after the unrestricted use of this ointment, untoward reactions are still fairly frequent. This is chiefly because the ointment is readily available without prescription and consequently laymen are likely to apply it freely without medical supervision. Caution in its use is advised even in the hands of the physician.

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BOOK REVIEWS AND NOTICES

FROM THIRTY YEARS WITH FREUD. By THEODOR REIK. Translated by RICHARD WINSTON. Pp. 241. New York: Farrar & Rinehart, Inc., 1940. Price, $2.50.

NEUROPSYCHIATRISTS had long recognized the permanency of distressing memories. Charcot had shown that hysterical manifestations were preceded by emotions due to accidents. Janet had taught that "traumatic memories," directly or indirectly, might later cause neuroses. The influence that these predecessors of Freud may have had upon his work, the author does not comment upon. Breuer, through hypnosis, was recalling in hysterical patients, experiences of which they had lost conscious recollection. Freud began to work with Breuer, but later departed in anger, and adopted "free association" as a better means of reviving forgotten memories. Instead of treating his subject logically, the author is emotionally dominated by his admiration for the Master whose name he believes imperishable, living "long after Hitler and Mussolini are dust." He is not a physician and agrees with Freud that others "had come closer to the fundamental truths of psychoanalysis than had the physicians." One is more nearly in accord with the author when he speaks of the masterful style employed by Freud in his writings, as exemplified in his "Dostoyevsky and Patricide."

N. Y.

PSYCHOTHERAPY. Treatment That Attempts to Improve the Condition of a Human Being by Means of Influences That Are Brought to Bear Upon His Mind. By LEWELLYS F. BARKER, M.D., Emeritus Professor of Medicine, Johns Hopkins University; Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 218. New York, D. Appleton-Century Company, Inc., 1940. Price, $2.00.

THIS small volume for general practitioners and intelligent laymen is by a physician who employs psychotherapy in conjunction with all other remedial measures. The methods of Freud, Janet, Adler, Jung, Rank, Stekel and Meyer are discussed as to their applicability either in functional or organic diseases, and in the various periods of childhood, adolescence, adult life and old age. Environmental and hereditary factors are regarded as of the utmost importance. It is the author's belief that proper psychotherapy will prove of ever-increasing importance. There is an informative glossary, an extensive bibliography and a good index.

N. Y.

PLAGUE ON US. By GEDDES SMITH. Pp. 365; illustrated. New York: The Commonwealth Fund, 1941. Price, $3.00.

A MEMBER of the staff of the Commonwealth Fund writes to other laymen about communicable diseases in a crisp and entertaining, yet clear and accurate, style that should bring heart-searching to many medical writers. Also the medical man as well as the layman will have much to learn from its contents. From the first chapter on the major plagues of history to the ninth and last, the Epilogue, and especially in the Epilogue one is constantly meeting important but generally overlooked facts, fresh points of view, and an occasional pregnant surmise. At a time when war is again causing large movements of the population of this country and severe epidemics

may be awaiting us as they did in 1918, this book's appearance is timely. From it, for instance, we learn almost the latest information about influenza —this is a front that is being pushed forward almost daily—and we are gratified to know that even if we are threatened with another severe epidemic, already we are much better equipped to meet the situation than we were in the last war.

Once more we are indebted to the Commonwealth Fund, both for stimulating the creation of this book and for presenting it to the public.

E. K.

THE JOURNAL OF CLINICAL ENDOCRINOLOGY, VOL. 1, NO. 1, JANUARY, 1941. Issued Monthly for The Association for the Study of Internal Secretions Pp. 90; illustrated. Springfield, Ill.: Charles C Thomas, 1941. Price: annual subscription, $6.50; single copies, $1.00.

THIS new journal is the second to be published by The Association for the Study of Internal Secretion. With the rapid growth of this subject in the past quarter century it has become necessary to divide the field, Endocrinology covering the experimental side of endocrine research, the new journal being devoted to the clinical aspects of the subject. The distinguished character of its Publication Board and Editorial Committee gives assurance that a high standard will be maintained. Thus does the romance period of endocrinologic literature recede still further into the obscurity of the past.

E. K.

DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS AND STERILITY. By CHARLES MAZER, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; Gynecologist to the Mount Sinai Hospital, Philadelphia, and S. LEON ISRAEL, M.D., F.A.C.S., Instructor of Gynecology and Obstetrics, School of Medicine, University of Pennsylvania; Associate Gynecologist to the Mount Sinai Hospital, Philadelphia. Pp. 485; 88 illustrations and 1 colored plate. New York: Paul B. Hoeber, Inc., 1941. Price, $6.50.

IN this volume presented by authors long known for their research in clinical and laboratory phases of endocrinology, the family physicians will find much to help him in the treatment of these frequent gynecologic complaints.

The text, which is divided into 30 chapters, begins with the normal physiology of the female reproductive system. The physiologic contrasts of estrogen and progestin are well brought out, while the dysfunctions of puberty are well arranged from the standpoint of treatment. The normal menstrual cycle and its phases, and the menstrual hormone balance are well correlated in a discussion of the synchronous changes in this interrelated phenomenon. The authors regard medical treatment of dysmenorrhea with scepticism, but mention agents of worth and include certain indications where insulin may have a beneficial effect. They regard the various types of cervical dilatation as of value only in producing pressure atrophy on nerve ends. Other types of surgery in dysmenorrhea are described. The authors regard low dosage irradiation to the pituitary glands and ovaries as the best treatment for exaggerated pre-menstrual tension. They discuss the physiologic approach in the treatment of migraine which has a close menstrual connection.

The debatable question of pre-menstrual breast changes is analyzed from both points of view. The authors recommend the inhibition of hypophyseal activity, the cause of a mazoplasia, by estrogen. Before proceeding to the subject of amenorrhea, a short section brings out the few known facts regarding vicarious menstruation.

Amenorrhea based on pituitary derangements is discussed at considerable length, and with profuse reference to the literature, under three headings: adiposogenital dystrophy (Froelich's syndrome), pituitary cachexia (Simmonds' disease), and pituitary adenomas. For these three dissimilar conditions there is a full correlation and evaluation of symptoms, physical signs and laboratory examinations, with a very satisfactory outline of treatment.

A similar handling of amenorrhea caused by primary ovarian derangements is followed by series of shorter chapters on the relationship of amenorrhea to dysfunction of the uterus, thyroid glands and both functional and organic derangements of adrenal glands and the nervous system. In considering the subject of hypomenorrhea three types are considered with appropriate therapeutic approaches.

The portion of the book which particularly appeals to the Reviewer and should be of much advantage to the general practitioner, for whom the book is intended, is the section dealing with various abnormal uterine hemorrhages. Each pathologic or functional factor is well described, and its influence evaluated together with means of diagnosis and treatment. Careful perusal of this section of the book and the application of the methods suggested should clear up the etiology of many cases and lead to appropriate and easily managed therapy. The large clinical experience of the authors is well reflected in their description of the dysfunctional bleeding of puberty and the menopause, and the appraisal of the hormonal therapy suggested in the literature, together with their own specific recommendations.

The second part of the book, on Sterility, discusses various pelvic lesions in the female recognized as frequent causes. Tubal patency and uterosalpingography are contrasted as to their value in diagnosis. The endocrine factors and endocrine treatment are well presented. The dual etiology of this condition is recognized in an excellent chapter by the authors on the male factors and equally good chapters on the diagnosis and treatment of male sterility by Dr. Charles W. Charny. It is interesting to note that tubal damage was a factor in 245 cases (55.9%) of their cases, while male infertility was responsible in 182 cases (41.5%). The authors stress the importance of germ plasm defects in the causation of habitual abortion. An interesting feature of the book is the appendix which lists the various commercial preparations of hormones, and their classification and unit values.

Such a fine recapitulation and presentation of the subject should be of interest not only to the specialist in gynecology, but also to the general practitioner. The plan of the book and the manner of presentation should be of special value to the family physician in the aid offered as to diagnosis and in the evaluation of various types of treatment suggested for the symptomatic conditions discussed. P. W.

DERMATOLOGIC ALLERGY. An Introduction in the Form of a Series of Lectures. By MARION B. SULZBERGER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University; Associate Attending in Dermatology and Syphilology, Montefiore Hospital, New York, etc. Pp. 540; 39 illustrations, 13 colored plates and 17 tables. Springfield, Ill.: Charles C Thomas, 1940. Price, $8.50.

Modestly called in the preface a primer, an introduction to dermatologic allergy, the volume falls little short of being the book of reference which it specifically claims not to be. Apparently, in committing his lectures to print, the author has allowed them to expand well beyond their original

scope. (One of the "lectures" runs close to 50 pages and would require nearly 3 hours to deliver.) In addition to this formidable dose of material, the troubles of the beginner are increased by a style that is given to excessively long and involved sentences. The Reviewer therefore suspects that a neophyte in allergy would find the book hard going. On the other hand, allergists, whether dermatologists or not, will find it very interesting and stimulating, for the author has taken a broad view of the field and, giving free rein to a vivid imagination, has dared to set down much that is speculative and conjectural, but suggestive of possible lines of development of the subject. Chapter headings include: definitions and classifications; the skin as a protective organ, the recorder and the possible originator of allergic changes; some fundamental phenomena of allergy and their significance; the investigation of individual cases; common allergic skin reactions and skin diseases; eczematous contact dermatitis; urticarial responses to skin tests; urticarial skin diseases, including atopic dermatitis; some manifestations of allergy in infectious diseases; allergy to tuberculin; allergy to fungi; allergy as the basis of cutaneous syphilis; allergy and allergic skin reactions in miscellaneous infections; drug allergy and drug eruptions; the future of allergy. There are appended a translation of von Pirquet's article in which he first proposed the term "allergy"; a list of substances and concentrations for patch testing; a table of criteria for determining the industrial character of a dermatitis; suggestions for the management of eczematous and urticarial dermatoses; a glossary. The illustrations are excellent. R. K.

THE RÔLE OF THE LIVER IN SURGERY. By FREDERICK FITZHERBERT BOYCE, B.S., M.D., Diplomate of the American Board of Surgery; Fellow of the American College of Surgeons; Visiting Surgeon: Charity Hospital of Louisiana at New Orleans, French, Mercy, and Southern Baptist Hospitals, Hotel Dieu and Touro Infirmary. Pp. 365; 44 illustrations and 25 tables. Springfield, Ill.: Charles C Thomas, 1941. Price, $5.00.

THIS monograph, which was awarded the quinquennial Samuel D. Gross Prize for research in surgery by the Philadelphia Academy of Surgery in 1940, is a worthy successor to the distinguished recipients of this award in former years. In it the author has included a reasonably full review of the literature as well as his own original work and has handled well the difficulties presented by a field which is being opened further almost month by month. The Reviewer received clearly the impression that the author was well aware of the fact that his subject was not static but was undergoing constant change, and felt that by his awareness and resulting comments he would stimulate further studies in this important field.

The monograph reviews the speculations concerning "liver" deaths and the "hepatorenal" syndrome, wisely retaining the quotation marks, but fully covering known means of combating these complications. Tests of hepatic function are discussed and while the Reviewer feels that the author is perhaps too optimistic about the information they afford, he agrees that it is well to use them for what they are worth.

The hepatic factor in thyroid disease and in non-biliary and non-hepatic disease is given the importance that is its due. These chapters should be read carefully by every general surgeon, for too frequently liver injury is considered only in relation to the surgery of the gall bladder and the bile ducts.

Exception must be taken to the author's views on ether irrigation of the common duct. It is not accurate to state that "If the occlusion of the common duct is caused by a stone, gravel or inspissated bile, patency can usually be achieved by introducing into the drainage tube equal quantities

of ether and alcohol (Pribram, 1935) and repeating the irrigation until the occluding substance is dissolved." The Reviewer does not believe with Pribram that irrigation of the common duct with ether is a substitute for careful exploration of the common duct. Certain stones are not dissolved by this method even under the best of circumstances. Lahey in particular has emphasized the necessity of careful common duct exploration in calculous cholecystitis and his results and those of many other surgeons are convincing as to the rationale of the procedure.

If this monograph is read carefully by the general surgeon it cannot help produce a more thoughtful and critical attitude toward the rôle of the liver in surgical disease and should result in the saving of many lives.

I. R.

THE MEDICAL REPORTS OF JOHN Y. BASSETT, M.D. The Alabama Student. With an Introduction by DANIEL C. ELKIN, M.D., Joseph B. Whitehead Professor of Surgery, Emory University. Pp. 62; illustrated. Springfield, Ill.: Charles C Thomas, 1941. Price, $1.50.

"An Alabama Student," one of the best and best known of Osler's biographic essays, has given John Y. Bassett of Huntsville, Ala., an enduring niche in the medical Hall of Fame. Bassett's two articles in Fenner's rare *Southern Medical Reports*, which led Osler to his study of Bassett, are here reprinted in full, together with Dr. Elkin's Introduction, concerning chiefly Fenner's connection with Bassett. An appendix gives further details of Bassett's life than were available to Osler, in a letter to Osler from Dr. C. H. Mastin, a pupil of Bassett's. Admirers of both Bassett and Osler will be glad to know this attractive little volume.

E. K.

MODERN DERMATOLOGY AND SYPHILOLOGY. By S. WILLIAM BECKER, M.D., Associate Professor of Dermatology and Syphilology, Kuppenheimer Foundation, University of Chicago, and MAXIMILLIAN E. OBERMAYER, M.D., Assistant Professor of Dermatology and Syphilology, Kuppenheimer Foundation, University of Chicago. Pp. 871; 461 text illustrations and 32 full color plates. Philadelphia: J. B. Lippincott Company, 1940. Price, $12.00.

THE authors have demonstrated their courage and initiative by producing a new type of textbook in the already over-textbooked field of dermatology. This work is written in a discursive and easily readable fashion for the general practitioner and the medical student rather than the specialist. The style is conversational and that of the amphitheatre; the format, in the form of a two-column page, makes for easier reading; the typography is excellent. Too much praise cannot be lavished on the half-tone illustrations, which are surpassingly good, and in a class by themselves. The color plates, however, despite the authors' oath of allegiance in their preface, demonstrate in the Reviewer's opinion exactly the contrary—namely, that color illustration is unnecessary in dermatologic textbooks, an added cost, and diagnostically a common nuisance. The special paper which such style of illustration requires, adds greatly to the physical weight and expense of what should be a convenient handbook.

Sixteen groups of topics in the field of dermatology are covered, and there is a section of 178 pages on syphilis, covering 20 topics. The authors do not profess to be encyclopedic. The dermatologic divisions of the table of contents indicate distinctive and interesting departures from conventional dermatologic textbook classifications, with a trend towards functional, as distinguished from morphologic background. This departure from conventional technique is one that the Reviewer regards as eminently desirable, and one is not therefore disposed to be too harsh with some of the odd juxtapositions which one encounters, as for example, the mixture

of symptoms, causes, and morphologic groups collected under "Papulo-squamous Eruptions" (p. 194). Under "Dermatoses of Physical Origin" one finds factitial eruptions which are expressions of psychoneurogenous functional disturbance. Erythema nodosum accompanies rosacea, a vaso-neurosis; and morphœa, also probably a disease of the nervous system, into the category of dermatoses of vascular origin.

This, however, is merely minor criticism. The emphasis on the functional throughout the work, and especially in the liberal space and enthusiastic interest given to the neurodermatoses, is a great advance to which the authors and their group have made notable contributions in literature and thought. Excellent sections, from the standpoint of the student and practitioner especially are those on pyogenic and mycotic infections of the skin. The authors have read into both their diagnosis and therapy many of those valuable practical hints and observational slants which are the best contribution of the individual expert to the commonsense and everyday practice in his field. The general material on anatomy, physiology and immunology is up-to-date, and men trained in the hematoxylin-eosin era of American histopathology especially can afford to read these sections with attention. The diagrams covering the cross-sections of the various elementary lesions of the skin have unusual teaching quality. The formulæ and the directions accompanying them should satisfy both student and practitioner who cannot take the time to indulge in reasoned extemporization. The sections on allergy, somewhat scattered, and the discussion of the toxic dermatoses of epidermal origin are an advance on most texts available in this country. References to the literature through this section of the book are abundant and well chosen. An exasperating phrase, "diagnosis is not difficult" recurs too frequently for a student-practitioner text.

The section on syphilis raises in the Reviewer's mind the question as to whether, in the light of the high degree of specialization that syphilology has reached in the last two decades, this topic should really form a part of dermatologic textbooks. It is impossible to present syphilis satisfactorily to the practitioner and student in a discursive and conversational way. The effect is sketchy and the sharp definition of principles, the precise figures and the now syphilologically accepted rules of procedure are blurred by over-emphasis on visible syphilids and unpardonabilities such as verbal and tabular differentiation on morphologic grounds of the chancre from other lesions on the genitalia. Even in a presentation such as this, though better balanced than the average, the description of tabes dorsalis and taboparesis occupies a little more than one page, while the picture of mal perforans occupies a full half-page. The Reviewer is almost convinced that a modern condensed textbook of diagnosis and treatment in syphilology intended for practitioners and students could be published without any illustrations whatever, and would indeed be the better for the lack. Only the extended and special texts or the single or multiple volume encyclopedia of the disease can afford such indulgence in history, orientation and illustration as is here presented. The differential table of chancre *versus* chancroid, which if printed at all should be as an illustration of what *not* to do under practice conditions, is not the only example of criticizable syphilology. A fairly careful search disclosed no description of the serologic follow-up of penile lesions, especially chancroid. The authors have accepted Coöperative Clinical Group results in almost everything else; but in their treatment systems (summarized on a special insert sheet) the internationally and nationally evaluated systems of treatment, for which precise numerical and percentage information as to procedure and results is available, apparently do not appear. In their place are methods of treatment, perhaps meritorious and deserving of consideration, but for which no evidence of perfor-

mance is supplied. Such material and its evaluation belong first in the current literature, and then under review in special texts, but should not form a part of a description of current treatment conceptions, especially in early, latent and congenital syphilis and syphilis in pregnancy, in which more thoroughly evaluated and endorsed procedure should be popularized. The references to the literature in the syphilologic section are not up to the standard of the rest of the work, and there are some mistakes in reference names which should be corrected in future editions. The emphasis on collateral public health and social hygiene factors in the control of syphilis is commendable and especially appropriate to a time of national emergency, with its characteristic venereal disease control problems.

Such critical comment as has been offered should not, however, obscure the fundamental interest and merit of this book. It is a new, courageous attack on the teaching problem of dermatology, embodying many originalities of approach, viewpoint and technique with superlative illustrations and genuine up-to-dateness in many fields such as functional disease, allergy and so forth, which form little or no part of the heretofore conventional texts for dermatologists themselves, not to mention medical students and practitioners. J. S.

METHODS OF TREATMENT. By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals, and EDWARD H. HASHINGER, A.B., M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals, and St. Luke's Hospital, Kansas City, Mo. With chapters on Special Subjects by 12 Contributors. Pp. 997; 138 illustrations. Seventh edition. St. Louis: The C. V. Mosby Company, 1941. Price, $10.00.

THE seventh edition of this well-known textbook is planned to furnish an outline of all the methods of treatment employed in internal medicine. The presentation is characterized by unusual clarity and, while the Reviewer's methods would differ from those of the authors in certain particulars, the book is a mine of information useful to anyone practising medicine. I. S.

BACTERIOLOGY IN NEUROPSYCHIATRY. A Survey of Investigations Concerned With the Specific Rôle of Infections and Immune Processes. By NICHOLAS KOPELOFF, PH.D., Research Bacteriologist, New York State Psychiatric Institute and Hospital, New York. Pp. 316. Springfield, Ill.: Charles C Thomas, 1941. Price, $4.50.

The purpose of this book, as the author states in the preface, is a presentation of the contributions which bacteriology and immunology have made towards the elucidation of nervous and mental diseases. The book is divided into four parts, dealing with diseases of known etiology with primary involvement, or secondary involvement of the central nervous system, with diseases of unknown etiology and finally with the immunology of the central nervous system. Current ideas and problems concerning etiology, diagnostic methods, symptomatology, immunology, prophylaxis, treatment and so forth are summarized; and an adequate bibliography of recent years is given to substantiate the various discussions. In the field of psychiatric disorders, infectious and toxic agents have frequently been considered as causative factors. Such reports are critically evaluated by the author in the light of present-day bacteriologic and immunologic knowledge. Although the single discussions are rather brief due to the limited size and the scope of the presentation it very well can be used as a reference book. W. H.

ACCEPTED FOODS AND THEIR NUTRITIONAL SIGNIFICANCE. Containing Descriptions of the Products Which Stand Accepted by the Council on Foods of the American Medical Association on September 1, 1939. Pp. 492. Chicago: American Medical Association, 1939. Price, $2.00.

EVERY physician is acquainted with the fine work that is being done by the Council on Foods of the American Medical Association. The Council now publishes descriptions of products which had been found acceptable by it, up to the time of going to press. The volume is an encyclopedic work arranged in chapters with a full table of contents and excellent indices; one of these lists the names of manufacturers and distributors; the other is the general index.

The first section concerns the history and purposes of the Council, the scope of its work and certain of its policies regarding fabricated foods. A brief section is devoted to vitamins and vitamin units. Here we find well illustrated the terse, comprehensive style which characterizes the whole volume. No important information seems to be left out and yet one feels that the few lines devoted to each of the vitamins gives a satisfactory description of its composition and uses.

The volume has inestimable value not only for the physician but to all other persons concerned with nutrition. More and more the doctor is consulted with regard to diets and their nutritional qualities. Especially is he likely to be asked about the relative value of one or another of the highly advertized fabricated foods. In this volume are given, briefly, but completely the valid information needed to answer all such questions.

The section on milk and milk products is especially timely and valuable because it is authoritative. One meets every day persons who say they do not believe in pasteurized milk. Nobody knows exactly what this means and especially can it be easily ascertained that the person who makes such a statement does not know what he means. The complete answer to all such primitive assertions is contained in less than seven lines of this volume.

"Pasteurization of Milk.—The pasteurization of milk is a public health measure. The public should demand pasteurized milk for drinking and the use of pasteurized milk in milk products. The dairy trade should universally adopt pasteurization in the interest of public health.

"There is no cogent evidence that pasteurized milk is significantly inferior nutritionally to raw milk."

The only possible criticism that could be offered concerns the size of type that has been employed; it is smaller than we like for general reading. The font appears to be that used in the *Journal* and the material is probably lifted out without being re-set. As a work which will be consulted chiefly for reference, however, this is not a serious objection.

It is difficult to think of any member of the community who would not derive benefit from the use of this volume. A. H.

TABER'S CYCLOPEDIC MEDICAL DICTIONARY Including a Digest of Medical Subjects—Medicine, Surgery, Nursing, Dietetics, Physical Therapy. By CLARENCE WILBUR TABER and 14 Associates. Pp. 1488; 273 illustrations. Philadelphia: F. A. Davis Company, 1940. Price, $2.50; thumb-indexed, $3.00.

BEGINNING 3 years ago as a "Digest of Medical Terms," then enlarged to a "Medical Dictionary" with some 600 pages and about 20,000 words, this work has now grown to be a "Cyclopedic Medical Dictionary" with nearly 1500 pages and over 50,000 words. This brings it up into the class of abridged dictionaries and as such should find a wide field of usefulness. Valuable features of the book include: concise descriptions of diseases, with their diagnosis, symptoms, treatment, diet and nursing; first aid measures; nursing procedures; food analyses and vitamin tables; tabulated anatomic data; and the equivalents in French, German, Italian and Spanish of a series of 373 questions and expressions useful in dealing with patients.

R. K.

FOREIGN BODIES LEFT IN THE ABDOMEN. The Surgical Problems, Cases, Treatment, Prevention: The Legal Problems, Cases, Decisions, Responsibilities. By HARRY STURGEON CROSSEN, M.D., School of Medicine, Washington University, and DAVID FREDERIC CROSSEN, LL.B., School of Law, Washington University, St. Louis. Pp. 762; 212 illustrations, including 4 color plates. St. Louis: The C. V. Mosby Company, 1940. Price, $10.00.

THE authors have written this book to emphasize to surgeons the danger of leaving foreign bodies in the abdominal cavity, and they outline the best plan of treatment for various types of such cases. They have searched the literature thoroughly and compiled statistics on practically every type of abdominal foreign body which has been reported.

In the first part, on sponges left in the abdomen, the symptoms and signs of this accident are presented and numerous cases cited to show the various end-results which may follow. The various methods of preventing the loss of sponges are mentioned.

Then follow chapters on various other types of foreign bodies, such as forceps, needles and so forth. The final part of the first portion of the book has to do with swallowed foreign bodies and the treatment of these cases.

The second portion of the book concerns the legal aspects of the subject. Various court actions and cases are analyzed. The question of the reliance on the sponge count, the final examination of the operative field and other such questions are discussed.

The book should be an excellent reference work in medico-legal cases and is probably of as much value to lawyers as to doctors. It is well illustrated, with excellent drawings and photographs. L. F.

NEW BOOKS.

America Organizes Medicine. By MICHAEL M. DAVIS, Chairman, Committee on Research in Medical Economics. Pp. 335. New York: Harper & Brothers, 1941. Price, $3.00.

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PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS.

UNDER THE CHARGE OF

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THE TREATMENT OF CIRCULATORY COLLAPSE AND SHOCK.

FAILURE of the circulation results from a variety of causes. The terms "circulatory collapse" and "shock" are applied to circulatory failure in which the heart is not primarily at fault. The heart cannot act as an efficient pump unless the venous inflow to it is adequate; it cannot pump out blood which it does not receive. In peripheral circulatory failure, it is assumed that the venous return is inadequate because of some disturbance in the peripheral circulation and that if the venous return were made adequate, the heart would function normally. Since many circulatory failures affecting the body as a whole which are not the result of inherent weakness of the heart muscle have been included under the term "shock," it is not surprising that authors writing on the subject have had difficulty in finding a definition of shock that satisfies all the workers in the field.

From the physiologic viewpoint, peripheral circulatory failure may be said to be present whenever the blood flow to the tissues becomes inadequate in the presence of a heart capable of sustaining a normal blood flow. From this definition, it is immediately obvious that the clinical picture of peripheral circulatory failure will show considerable variation, depending upon the etiology of the circulatory failure and upon the nature of the many compensatory reactions which may occur in the body. Homans[17] summarizes the clinical picture of shock as follows: "(1) An appearance of pallor, sometimes associated with slight cyanosis; (2) a cold, moist, or sweaty skin; (3) a rapid, regular but thready pulse; (4) rapid, usually shallow respiration; (5) restlessness and an appearance of anxiety which may change under unfavorable circumstances to dulness and lessened sensitivity; (6) thirst; (7) a variable amount of nausea and sometimes vomiting." To this picture there are many exceptions.[9,26,36b] Some patients do not show pallor or lividity; in others the blood pressure is well maintained; in still others

the heart rate is not increased—indeed, it may be slower than normal. In other patients mental dulness may be absent. Thirst is quite commonly absent. The rectal temperature may be elevated.

In the literature there is frequently no clear-cut distinction made between collapse and shock.[9] It has been suggested that the terms "primary shock" or "collapse" be applied to sudden short-lived insufficiency of the peripheral circulation, and that the terms "secondary shock" or "shock" be used when the circulating insufficiency is more prolonged.[5,8,11,36b] This distinction has not been in general use. Nevertheless, it is a useful one, because the prognosis and therapy of sudden transitory insufficiency of the circulation is frequently different from that of more prolonged peripheral circulatory failure. The term "collapse" is preferred to "primary shock" because it is more general. Primary shock associated with wounds is one type of collapse. In this paper, the term "peripheral circulatory failure" will include all examples of generalized circulatory failure in which the heart is capable of functioning normally. "Circulatory collapse" will include all forms of sudden, short-lived peripheral circulatory failure; "shock" will include the cases of peripheral circulatory failure of longer duration.

The Mechanism of Peripheral Circulatory Failure. Investigators agree that the fundamental mechanism of peripheral circulatory failure is a disproportion between the circulating blood volume and the size of the vascular bed.[5,8,27,31,36b] This disproportion may occur in two ways: 1, because of a decrease in the circulating blood volume so that the vascular bed is not filled; and 2, because of an increase in the size of the vascular bed so that the normal blood volume does not fill the dilated vascular bed. This vasodilation may result from fever, infection, drugs, or it may be of reflex origin. In any case, the venous return to the heart becomes inadequate and the cardiac output decreases.

Circulatory Collapse. Acute transient peripheral circulatory collapse is very common.[23,36a] It may occur in normal subjects at the sight of blood, during a venipuncture, or if the subject is hurt or becomes nauseated. It frequently occurs in ambulatory patients who have had a cold or infection; in the hospital it is seen in patients with pneumonia or other infections who sit up to use the bed-pan, or in persons who stand up too soon after a bout of fever or after the loss of blood. It occurs from time to time when acutely ill patients are moved, or it may be precipitated by palpation of a tender abdomen. Regardless of the precipitating cause, the clinical picture is the same. The patient becomes deathly pale, breaks out in a cold sweat, and complains of epigastric distress and nausea. The field of consciousness becomes narrowed, objects become hazy and dark, and the subject may lose consciousness. At the onset of the attack, the heart rate usually becomes rapid, but as the arterial pressure falls, the heart rate frequently decreases. At the height of the collapse, the heart rate may be approximately 40 and the radial pulse impalpable. If the subject is held in the upright position, he may develop clonic movements of the arms and legs.

Circulatory collapse in these cases results primarily from pooling of blood in a dilated circulatory bed.[36c] The blood volume is not decreased in the normal subject with circulatory collapse precipitated by unpleasant visual stimuli, pain or nausea. The marked fall in arterial pressure

indicates that the peripheral vascular bed has dilated so that the normal blood volume no longer fills the dilated vascular bed and the venous return to the heart becomes inadequate. There are two factors operative in this type of collapse. The first one is gravity; the second is the stimuli to the central nervous system. When the patient is in the upright or sitting position, the venous pressure in the parts of the body below the heart is increased by the force of gravity. This increased venous pressure makes the cross-section area of the venous bed below the heart larger when the patient is in the upright position than when he is in the recumbent position. When the tone of these vessels below the level of the heart is suddenly decreased as a result of stimuli from the brain, the blood drains into the dilated vessels, the venous return to the heart becomes inadequate and arterial pressure falls precipitously. The resulting cerebral anoxia may produce unconsciousness.

In the circulatory collapse induced by sodium nitrite[37,38] or by infection,[32] the same two factors are operative, namely, the force of gravity and the relaxation of the venous side of the circulation. In these cases the loss of venous tone is probably the result of the action of the drug, or of the infection, on the veins and venules. Under such circumstances, when the patient is in the upright or sitting position, more than the normal amount of blood is pooled in the relaxed venous system and circulatory collapse may result. Studies of this type of circulatory collapse have shown that the arterioles are constricted to compensate for the decrease in effective blood volume, and that further arteriolar constriction by drugs is not helpful.[32,39]

If the blood volume is decreased by hemorrhage, vomiting, or loss of plasma into the peritoneal cavity, circulatory collapse may occur when the patient sits up. In these cases the venous tone may not be decreased. When the patient is in the erect or sitting position, the shifting of a normal amount of blood into the lower portion of the body may decrease the venous return to the heart sufficiently to produce circulatory collapse.

In certain patients a similar type of collapse occurs in the recumbent position. Subjects who are bled when they are in the recumbent position may develop collapse which lasts for only a short time, and from which they may recover without any demonstrable increase in blood volume.[12] Palpation of the abdomen in a patient with acute pancreatitis may repeatedly precipitate collapse. In these patients the development of collapse may be of more serious import than in patients in whom circulatory failure is precipitated by gravity.

Patients frequently develop circulatory collapse after spinal anesthesia.[10,24,30] This is the result of vascular relaxation in the lower extremities and splanchnic areas. This relaxation includes the arterial as well as the venous side of the circulation. The dilated vascular bed pools blood and decreases the venous return to the heart.

In the treatment of circulatory collapse, it is important to make use of gravity in aiding the venous return to the heart. The patient is placed in the recumbent position, and if possible, the foot of the bed is elevated. In most instances this will produce a rapid increase in the arterial pressure and the pulse will become of good volume. The slow pulse which is frequently observed at the height of collapse is the result and not the cause of collapse.[23,36a] It is of vagal origin and is

caused either by reflex stimulation or by direct stimulation by anoxemia of the vagal centers in the brain. Atropine will prevent slowing of the pulse but will not prevent circulatory collapse.[23] In the treatment of collapse which may occur soon after the induction of spinal anesthesia, the head-down position is contraindicated if the anesthetic used has a specific gravity greater than that of the spinal fluid. The Trendelenburg position may be used, however, after sufficient time has elapsed to allow most of the anesthetic drug to be fixed in the tissues.[30]

Drug therapy is frequently not needed because recovery may be quite rapid. In patients with severe infection or with a considerable decrease in blood volume, recovery of the circulation may be much slower. If pain is present, morphine sulphate in 15 mg. doses is useful. Except in collapse occurring during spinal anesthesia, the arterioles are usually constricted, and drugs which accentuate this constriction without increasing the venous return are usually ineffective in preventing the onset of collapse.[33,39] In laboratory experiments,[19] paredrinol sulphate, a drug that increases the venous tone, when administered in doses of 25 mg. intramuscularly or 30 to 50 mg. orally, has been effective in preventing the onset of this type of collapse. Epinephrine and pitressin were ineffective.[33,39] During spinal anesthesia, ephedrine sulphate, given subcutaneously in doses of 25 to 50 mg., is at least partially effective in preventing a drop in blood pressure.[24] Altschule and Gilman[1] have reported that paredrine given intramuscularly in doses of 10 to 20 mg. is likewise effective in preventing a drop of blood pressure during spinal anesthesia.

Shock. More prolonged failure of the peripheral circulation produces the classical clinical picture of shock. In collapse, the duration of the circulatory insufficiency is short; in shock, it is more prolonged.[8,36a,b] It is generally agreed that in shock the circulatory failure is frequently related to a decrease in blood volume as a result of external hemorrhage, dehydration, or loss of plasma into the peritoneal cavity or into traumatized tissues. In addition, many observers believe that infection and the breakdown products from injured tissues play an important rôle, not only in causing pooling of blood by vasodilation, but also in producing a decrease in plasma volume by increased capillary permeability. There are several monographs which give good reviews of the current opinions on etiology of shock.[5,8,27,31]

From the clinical point of view, it is essential to remember that the infection must be prevented if possible, and that if present it must be combated with all the means at our disposal. In addition, the blood volume must be kept at an adequate level. Hematocrit determinations and serum protein determinations on venous blood collected without stasis are useful in following cases of hemorrhage, trauma, peritonitis, burns, diarrhea, vomiting, and intestinal obstruction. The protein concentration can easily and quickly be calculated from the specific gravity of the serum by the falling drop method.[2,18,31] In simple dehydration, which is present in patients with diarrhea or vomiting, there is a rise in the hematocrit reading and in the protein concentration of the plasma. After hemorrhage there is a decrease in both the hematocrit reading and in the protein concentration. If a fluid rich in protein is lost from the blood stream, the hematocrit reading rises and the protein shows only a slight increase, or it may even

fall. This may occur in burns, peritonitis or trauma. If hemorrhage is complicated by dehydration, the hematocrit reading may be low and the protein concentration increased. In essence, an attempt is made to keep the hematocrit reading and protein concentration of the blood within normal limits. They must both approach the normal at the same time. For example, after a severe burn, the hematocrit reading may be very high and the protein concentration normal. If the hematocrit is restored to normal by the intravenous injection of saline, the protein concentration will be too low. Such patients need protein as well as fluid.

In acute infections the blood volume is usually not decreased unless the patient is dehydrated. If the patient's kidney function is normal, dehydration will not occur if sufficient fluids are given to keep the urine specific gravity below 1.012. In such cases no further information as to the state of hydration will be obtained from a knowledge of the hematocrit reading or protein concentration.

The importance of the laboratory aids in maintaining an adequate blood volume has been recently reëmphasized by Scudder.[31] These laboratory tests are important because they demonstrate the changes in blood volume before they can be detected by clinical observations. It has long been recognized that the fall in arterial pressure may be a late sign in peripheral circulatory failure. As the blood volume decreases, the pressure may be maintained by peripheral arteriolar constriction. In this way, the blood flow to the tissues may be inadequate in the presence of a normal blood pressure. If the arterial pressure falls in spite of peripheral constriction, the prognosis is grave unless the pressure can be raised. In certain instances associated with infection, the arterial pressure may fall primarily as the result of vasodilation. In these patients the peripheral flow may remain adequate and the prognosis is better.[32,36b]

If hemoconcentration is present, as indicated by a rise in both the hematocrit reading and protein concentration, the fluid intake should be increased either by mouth or parenterally. In these cases normal saline is adequate. If hemorrhage has occurred, transfusions of whole blood are indicated. Unless the anemia is profound, or unless there is concomitant lung disease, it is more important to restore the volume of blood than to restore the erythrocyte concentration. Therefore, even after moderately severe hemorrhage, plasma may be as satisfactory as whole blood in restoring the circulation. Although after hemorrhage physiologic saline may produce a lasting improvement in the clinical signs and symptoms, the blood volume will remain decreased until the body has added protein to the plasma.[12]

In cases in which protein is being lost into the tissues or into the peritoneal cavity, as indicated by an increase in hematocrit reading out of proportion to the rise in protein concentration, saline is not effective in maintaining a normal blood volume because of its diffusibility.[3] The fluid added to the blood stream must contain either protein or a substance that is not diffusible through the normal capillary walls and that has an osmotic pressure comparable to that of the normal plasma proteins. Whole blood or plasma are the ideal fluids. In civilian life whole blood has been satisfactory. Recently much work has been done on the use of serum and plasma transfusions in

shock.[6,20,22,25,29,34,35] Experimental work has indicated that serum and plasma are satisfactory in maintaining the blood volume. Both serum and plasma can be preserved by drying them from the frozen state ("lyophile" process).[13,15] It has been suggested that the reactions following the intravenous administration of "lyophile" serum are the results of the use of serum and not of a change induced by the process of desiccation. "Lyophile" plasma produced no reactions.[34] Other authors state that plasma and serum can be used interchangeably and that properly prepared serum does not produce reactions.[4,16]

Strumia, Wagner and Monaghan[34] have recently summarized the advantages of citrated blood plasma as follows: "(*a*) It can be readily prepared and safely transported, (*b*) it can be stored for an indefinite period of time, (*c*) it is entirely safe and free from reactions, (*d*) it can be used in large and repeated doses, (*e*) it is ready for instant use, and (*f*) it does not add to concentration of erythrocytes if this condition is present."

It is generally agreed that pooled plasma or serum can be given intravenously without typing. Levinson and Cronheim[21] observed that large pools of serum never showed rich agglutinin content, whereas many of the individual serums that made up the pool possessed a high agglutinin titer. They concluded that there is neutralization of agglutinins *in vitro* when different groups of serum are mixed, and they suggested that serum or plasma prepared for transfusion be made up of pools containing all blood groups. In addition, they stated that neutralization of agglutinins by both tissue and serum of the recipient provides a wide margin of safety in protecting the recipient's red cells from the infused agglutinins.

Cannon[8] emphasizes that in traumatic shock, in contrast to collapse, there is little or no improvement from elevation of the foot of the bed. This is true in many cases of shock, but not in all. Patients in shock in whom the arterial pressure is maintained by peripheral vasoconstriction are very prone to sudden episodes of circulatory collapse associated with pain or change in position. Elevation of the foot of the bed in these patients will immediately result in an improvement in the clinical picture.

All observers in the World War[8] emphasized the importance of keeping the patient warm and, in the case of broken bones, the necessity for splinting and immobilization before moving the patient. In civilian practice, the importance of treating shock before moving the patient for Roentgen ray examination or before undertaking any operative procedure is universally recognized. Cannon[8] stresses the importance of restoring the blood volume before using an anesthetic, and points out the danger of even slight anoxemia in cases of shock. In his experience with patients in shock, ether was a more dangerous anesthetic agent than nitrous oxide and oxygen.

With the exception of morphine for the relief of pain, drug therapy has not proved to be very useful in the treatment of shock. Paredrinol and ephedrine, which have proved to be useful in collapse, have not been shown to be of definite value in shock. Neither epinephrine nor pitressin has been useful in either clinical or experimental shock.[5] In patients with respiratory depression, coramine and caffeine have proved to be useful as respiratory stimulants, but they have not been shown

to have much effect on the circulation itself. Strychnine has been recommended from time to time, but its usefulness has never been clearly demonstrated in cases of shock. More recently desoxycorticosterone acetate or extracts of the adrenal cortex have been used in the treatment of shock.[14,28,31,40] While it is clear from experimental work that adrenalectomized animals have a decreased blood volume and may have peripheral circulatory failure, evidence is lacking to prove that patients in shock are deficient in cortical hormone. As yet there are no clear-cut experiments demonstrating that cortical extract of the adrenal glands or desoxycorticosterone is useful in the treatment of shock, except in those cases in which the adrenal cortex is clearly deficient, *i. e.*, in adrenalectomized dogs or in subjects with Addison's disease.

The slow circulation and prolonged tissue anoxia produce the following secondary changes in the body:[8] the venous blood contains little oxygen; the carbon dioxide combining power is reduced because of tissue acidosis; the basal metabolism is decreased. The changes in serum potassium reported by Scudder probably belong in this group.[31] In the past, treatment of these secondary changes has not been successful. Recently Boothby, Mayo and Lovelace[7] have reported that the administration of 100% oxygen is a useful adjunct in the treatment of shock.

Terminal Circulatory Failure. If trauma is severe enough, or if infection cannot be controlled, the circulation eventually fails, regardless of treatment. In this terminal picture, hemoconcentration plays little part because it will occur even if the blood volume is maintained by continuous transfusion. The relative importance of the central nervous system, of the peripheral vascular system, and of the heart in this terminal picture is not clear. This problem needs to be elucidated by more clinical observations.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MARCH 18, 1941

Action of Crystalline Pepsin on Diphtheria Antitoxin and Pneumococcus Antibody from the Horse. A. M. PAPPENHEIMER, JR., and MARY L. PETERMAN (Department of Bacteriology, University of Pennsylvania, and Department of Pharmacology, University of Wisconsin). Purified antitoxic pseudoglobulin of high antitoxin content was digested with crystalline pepsin at pH = 4.2 and the specific precipitate formed with pure diphtheria toxin was dissociated with crystalline pepsin according to the methods of Pope (Brit. J. Exp. Path., **20**, 132, 201, 213, 1939). The normal antitoxin molecule undergoes the following changes upon digestion with the enzyme: 1, the molecular weight changes from 184,000 to 113,000; 2, the splitting occurs in a plane normal to the long axis; 3, the digested molecule combines with 45% more toxin per milligram than the normal antitoxin; 4, the carbohydrate content of the digested molecule is about 45% higher than normal antitoxin.

Several euglobulin preparations of horse pneumococcus antibody of various types, examined in the standard Svedberg oil turbine ultracentrifuge, showed wide variations in sedimentation constants. The basic unit of pneumococcus antibody in the horse appears to have the same sedimentation constant as normal serum globulin but the molecule tends to aggregate end to end. The amount and extent of aggregation varies in different animals. Both heavy and normal size antibodies have been broken down with pepsin by the method of Graber (Compt. rend. Soc. de Biol., **207**, 807, 1938). The digested antibody combines with about twice as much polysaccharide per milligram as the normal antibody and has a sedimentation constant of 5.2×10^{-13} cm./sec./dyne, suggesting a molecular weight less than 100,000. Pepsin-digested horse pneumococcus antibody is quite soluble in water and is

not precipitated by dialysis against distilled water to the same extent as is the normal antibody. It is also soluble in 0.35% saturated ammonium sulphate in contrast to normal antibody, but may be precipitated by half saturated ammonium sulphate. Almost all preparations were analyzed quantitatively for antibody content by the methods of Heidelberger and Kendall (Bact. Rev., **3**, 49 1939) and in many cases salt-dissociated antibody of high immunological purity was studied.

Effects of Direct Chemical Stimulation of the Respiratory Center. JULIUS H. COMROE, JR. (Department of Pharmacology, University of Pennsylvania). In an attempt to localize the respiratory center by means of a natural chemical stimulus, minute amounts (2 c.mm.) of chemical substances were injected directly into the brain stem in 80 cats through a fine steel needle, 0.5 mm. outside diameter, fixed in the Horsley-Clarke stereotaxic instrument.

The chemical stimulus employed was a 1.3% solution of $NaHCO_3$ in distilled water, buffered with CO_2 to pH 7.4 so as to have a CO_2 tension of 250 mm. Hg. The typical response to this solution was an immediate increase in both rate and depth of respiration; control injections of hypertonic or hypotonic saline and distilled water produced no response. More than 750 injections of this CO_2-bicarbonate solution were made in the pons and medulla up to the level of the inferior colliculus; consistent responses were obtained only in the medulla in the region of the formatio reticularis. These experiments add strong confirmation to previous localizations obtained by other methods (electrical stimulation, progressive sectioning of pons and medulla).

Other substances injected were HCl and lactic acids (N/1000, N/100, N/10) which rarely led to respiratory stimulation and then only minimally; saline solutions, equilibrated with CO_2 at 70, 300 and 700 mm. tension, which never stimulated; and 1.3% $NaHCO_3$ solutions (unbuffered, pH 8.0), which stimulated regularly.

Since (*a*) the failure of acid to stimulate cannot be attributed always to cell destruction (for, in some instances, CO_2-bicarbonate solution injected at the same point a minute later produced definite hyperpnea), and (*b*) high CO_2 tensions alone do not stimulate, it is suggested that the characteristic stimulus to the respiratory center is not "intracellular acidity" as is currently believed, but rather the HCO_3 ion, acting either by itself or in combination with CO_2.

Estimation of Total Base in Serum by Means of Measurements of Conductivity and Specific Gravity. F. WILLIAM SUNDERMAN (Department of Research Medicine and the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania). Analyses of the [total base] in serum were correlated with measurements of the conductivity and specific gravity of the serum. The conductivity measurements were made by means of a modified "sugar-ash" bridge utilizing a 60-cycle 110-volt alternating current and a special type of pipette cell. From a statistical analysis of the three variates by partial regression the following formula was derived:

$$\text{Total Base /mEq per L} = 8.62\ \text{SpC} + 0.06\ \text{G} + 27.26$$

where SpC represents the specific conductivity and G is equal to (specific gravity $20°/20° - 1.0000$) 10^4.

The standard deviation of the percentage differences between the calculated and analyzed values for total base in serum calculated from 46 observations is 1.9. The method is so simple and economical of both time and material that it would seem to afford a method of choice for clinical studies.

Pituitary-Diabetes in the Cat Treated by Low Diet, Insulin and Phlorhizin. F. D. W. LUKENS, F. C. DOHAN and M. W. WOLCOTT (The Cox Institute, University of Pennsylvania). Pituitary-diabetes in the cat has been described in a preliminary report. It was found that if insulin treatment was begun within the first 3 months of diabetes (when the islands showed hydropic degeneration), morphological restoration of the islands and functional recovery of the animals occurred. Recovery by means of insulin was not limited by the severity of the diabetes, but only by its duration, *i. e.*, by the development of irreversible lesions of the islands such as atrophy and hyaline change.

The response of diabetic animals to a reduction in diet has recently been observed. Two cats with very mild diabetes have recovered after 24 and 26 days on a low diet. On resuming the full diet they gained weight and the blood sugar remained normal. On the other hand, 5 cats with moderately severe diabetes have not been controlled by a similar reduction in diet. In contrast to insulin, dietary treatment is greatly limited by the severity of the disease. Finally, 2 diabetic cats have recovered following the administration of phlorhizin in moderate dosage for 2 to 3 weeks. The similarities and differences of these three experimental conditions (low diet, insulin, phlorhizin) have been considered. They permit an analysis of the gross conditions essential to the recovery of hydropic islands of Langerhans and of early diabetes.

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